



# THE KIDNEY IN HEALTH AND DISEASE

IN CONTRIBUTIONS BY EMINENT AUTHORITIES

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## PUBLISHERS' NOTE

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THIS volume is the outgrowth of a symposium on the structure and function of the kidney in health and disease which took place in Minneapolis during the summer of 1930. The project was initiated by Dr. Hilding Berglund, then Professor of Medicine in the University of Minnesota, and the social and financial responsibilities of the occasion were met by that institution. The programs were arranged and the speakers selected by Dr. Berglund, and the success of the undertaking was largely due to his energy.

The original plans included the publication of this material as soon as possible after the end of the symposium sessions, and a large part of the work of assembling and editing it was done by Dr. Berglund during the following year. To the great regret of all those concerned, his return to Sweden prevented him from finishing this aspect of the work.

The Publishers became convinced that these contributions are sufficiently important to be preserved in permanent form, that collectively they constitute a comprehensive and authoritative exposition of our present knowledge concerning a most important but still obscure field of medical science. For the purposes of the present volume the participants in the symposium have revised their contributions and amplified them to some extent to bring them up to date. Several contributions which were not included in the symposium have been added. The editorial work has been completed by Dr. Medes, with assistance from several of the contributors.





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# THE KIDNEY IN HEALTH AND DISEASE

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## PART I ANATOMY AND PHYSIOLOGY

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### CHAPTER I

#### THE FORM AND STRUCTURE OF THE MAMMALIAN RENAL TUBULE

By G. CARL HUBER, M.D., Sc.D.

**Introduction** —The relatively complex form and structure of the renal tubule of vertebrates has made of it for over a century the subject of repeated investigation. The difficulty of correlating structure and function has added to the interest of such studies and has called forth a long succession of physiological and pharmacological contributions of note. Repeatedly both morphological and correlated functional studies appear to have led to definite conclusions only to find through further investigations that such conclusions were subject to revision. Interest is further added by the fact that both phylogenetically and ontogenetically considered the renal organs of vertebrates consist of three successive sets of excretory organs known as pronephros, mesonephros and metanephros, the pronephros functions in the lowest vertebrates and during larval stages of amphibia, the mesonephros in fishes and amphibia and the metanephros in reptiles, birds and mammals. The renal tubules of the phylogenetically serial excretory organs, while successively more complex, are fundamentally of very similar morphology and structure and appear in the main to function similarly, cognizance of which fact is taken in experimental work in that it is possible to transfer deductions drawn from observations made on the simpler renal tubules of the amphibia to the more complex and less accessible renal tubules of mammals. The similarity of form, structure and function of the renal tubules of the



## 2 FORM AND STRUCTURE OF MAMMALIAN RENAL TUBULE

pronephros and mesonephros to those of the metanephros necessitates a brief consideration of the former in anticipation of a further consideration of the renal tubules of the metanephros in its fullest development as in the mammal. By means of the Born wax plate method of reconstruction it was possible to build up in wax at a magnification of 400 diameters the pronephric tubules of a larval

to mount in semipermanent form the renal tubules of birds and several mammals. Thus it is now possible to treat of the form and length of the vertebrate renal tubule in a much more satisfactory and comprehensive manner than was possible before such studies were undertaken. The figures here given are based on actual preparations and are not to be regarded as diagrams or semidiagrammatic representations. The measurements of length given are based on measurements made on models or on completely isolated and mounted renal tubules.



FIG. 1.—Reconstruction of the pronephric tubules of a larva of *Bufo* having a total length of 10 mm. *nephrost.* Nephrostomes; *ct.* common collecting tubule;  $\times$  region of the Y-shaped junction of the two tubules.  $\times 50$  (Huber Cowdry's Special Cytology, courtesy of Paul B. Hoeber, Inc.)

### PRONEPHRIC TUBULES

As a type of a functional pronephric tubule there is here depicted (Fig. 1) a wax reconstruction of a pronephric tubule of a larval toad of 10 mm in length. The tubule shown presents two nephrostomes opening into the coelomic cavity and lined by cells with prominent cilia. The tubules leading from the nephrostomes join in a Y-shaped junction. The tubule thus formed has a length of 2.5 mm and presents a series of loops which in the main extend in a cranio-caudal direction. The tubules reconstructed have their beginnings in nephrostomes and not in renal corpuscles with glomerular capillaries. The epithelium lining the coiled portion of these tubules is of a low columnar type presenting a typical and prominent brush border while the protoplasm of the basal part of the cell

shows a vertical striation which appears to be due to the presence of coarse cytotreticular fibrils. Von Mollendorff<sup>15</sup> has shown, in experiments with vital staining with trypan blue, that the coloring matter found in the lumen of the tubules appears in globular form in the cells with brush border. The evidence presented seems to substantiate the contention that water and contained substances in solution are absorbed into the blood through the epithelial cells with brush borders lining the coiled portions of the tubules. This portion of the pronephric tubule may thus be homologized with the tubular segment known as the proximal convoluted tubule of higher forms.

### THE MESONEPHRIC RENAL TUBULE

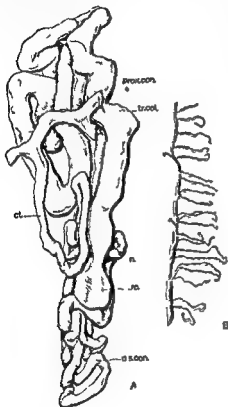
The mesonephric tubule has been known for many decades and was quite accurately described and figured by Nussbaum<sup>16, 17, 18</sup> based on observations made on teased preparations. The figures here given (Fig. 2) represent drawings of a model made by Horn wax plate method and casts of the lumen of collecting tubules made after an especially devised celluloid-alkalin injection method. The main efferent duct of the frog's kidney, the ductus deferens, joins the kidney at its caudal end and passing along its dorso-lateral border reaches the cephalic end where it becomes partly embedded in the kidney substance. At fairly regular intervals there empty into the ductus deferens at nearly right angles a series of transversely coursing collecting ducts embedded in the kidney substance near its dorsal surface. Into these nearly parallel transversely coursing collecting ducts there empty the mesonephric renal tubules in quite regular serial order. One such transverse collecting tubule with the terminal portion of a series of renal tubules is shown.

in w  
part

The tubule begins in a renal corpuscle and ends in a transverse collecting duct and has a total length of 7 mm. The renal tubules traverse the entire dorso-ventral thickness of the frog's kidney, the great majority of the renal corpuscles form an irregular layer situated near the ventral surface. Each renal tubule begins in a relatively large renal corpuscle of flattened oval form and averaging about 100 $\mu$  in diameter and consisting of a glomerular capillary complex and an invaginated glomerular capsule presenting a visceral and a parietal layer, the latter joining the renal tubule by means of a short neck. The visceral and parietal layers of the glomerular capsule are lined by a delicate layer of flattened pavement epithelium while the neck is lined by relatively short non-pigmented cells supporting long cilia. The neck is followed by a tubular segment having relatively large diameter and extending toward the

#### 4 FORM AND STRUCTURE OF MAMMALIAN RENAL TUBULE

dorsal surface of the kidney, there to form several bold loops which may extend to about the middle of the kidney substance. This tubular segment constitutes the proximal convoluted portion and



in the tubule shown in the figure presents an average diameter of  $75\ \mu$  and a length of approximately  $3.8\ \text{mm}$ , and is lined by an epithelium of low columnar form with finely striated superficial brush border and relatively distinct basal striations apparently due to the presence of fine granules in the cytotecticulum. The proximal convoluted portion is followed by a short and narrow segment ( $0.2\ \text{mm}$ ) comparable in position to the medullary loop of the mammalian renal tubule, and is lined by a low epithelium with delicate cilia. The succeeding tubular segment which has been termed the distal convoluted portion, attains a length of approximately  $2.5\ \text{mm}$  and an average diameter of  $30\ \mu$  and presents numerous coils and loops certain of which reach the ventral surface of the kidney and are lined by a low cuboidal epithelium presenting basal striations. A short junctional tubule unites this distal convoluted segment with a

transverse collecting tubule. This junctional tubule is lined by a cuboidal epithelium similar to that lining the collecting ducts. It is of interest to note that among teleosts are found forms whose kidneys possess very few or no glomeruli. Such forms have been subjected to careful investigation both morphologically and func-

tionally relatively recently by Edwards,<sup>4,5</sup> Grafflin,<sup>7</sup> and Marshall.<sup>11</sup> Edwards has shown that in an aglomerular kidney the mesonephric tubule is composed of three segments the first of which is similar to the proximal convolution of the higher vertebrates the second to the distal convolution and the third to a collecting duct.

### THE METANEPHRIC TUBULE

A description of the metanephric renal tubule requires consideration of the renal tubules of reptiles, birds and mammal. The metanephric tubules of reptiles and birds will receive brief consideration before entering on a more detailed discussion of the mammalian renal tubule.

**Reptilian Metanephric Tubules** The account of the morphology of the reptilian metanephric tubule is based on reconstruction and celluloid corrosion injections of the renal tubules and the duct system of a turtle (*Alligator mississippiensis*), garter snake and a lizard. The reconstructions made of the renal tubules of the several forms studied show such great similarity except for unimportant differences in size and extent of looping that a description of one of them obviates the necessity of describing the others. The account here presented is based on the metanephric tubule of a turtle (*Chrysemys marginata*) illustrated in 1 of fig. 3. The renal tubules of *Chrysemys marginata* begin in relatively small renal corpuscles averaging approximately  $30\mu$  in diameter consisting of a relatively simple glomerulus enveloped by a glomerular capsule with visceral and parietal liver the latter continuing as the neck, a short and narrow segment lined by an epithelium bearing long cilia. The renal corpuscles are centrally placed in pseudolobules of kidney substance. The neck is followed by the

lined by a striated epithelium which in position is the homologue of the medullary loop of the mammalian renal tubule. This segment is followed by the distal convoluted portion presenting a length of approximately 1 mm and an average diameter of  $40\mu$  and lined by a low columnar epithelium with striated protoplasm. A short junctional segment unites the renal tubule to a primary collecting duct. The total length of the renal tubule figured in 1 of fig. 3 is approximately 3.3 mm.

## 6 FORM AND STRUCTURE OF MAMMALIAN RENAL TUBULE

**The Metanephric Tubule of Birds**—In the study of the renal tubule of birds use was made of the kidneys of adult chicken *Gallus domesticus*. Use was made of especially devised methods of maceration and teasing. The material was prepared for teasing by injecting the fresh kidney through the renal artery with a 75 per

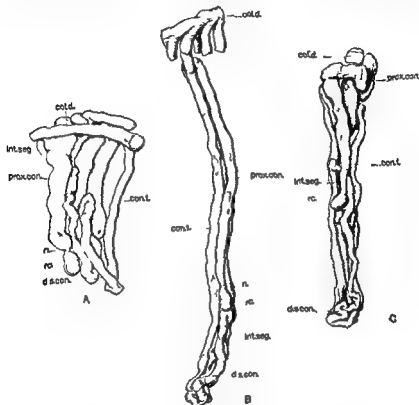


FIG. 3.—Reptilian metanephric renal tubules. A. Reconstructed from the kidney

of Paul B. Hoeber, Inc.)

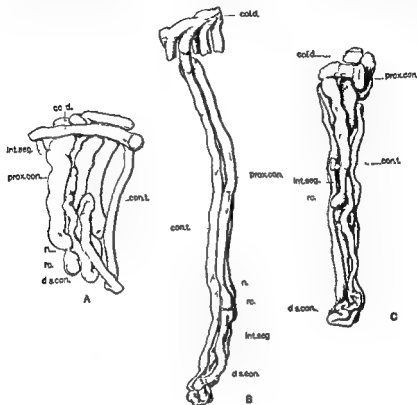
cent solution of hydrochloric acid at a pressure of about 20 pounds. After the injection the tissue was placed in strong hydrochloric acid for several hours and then thoroughly washed in water stained in hematoxylin solution and prepared for teasing. With adequate maceration it was found possible to isolate entire renal tubules attached to portions of the duct system and to mount such preparations in a semipermanent way ready for study under the micro-

scope. The kidney of the bird is an elongated, distinctly lobulated organ, with the ureter passing on the ventral and meso-ventral side, prominent branches passing from the ureter to the several lobules. The central portion of each lobule may be divided into a cortical and a medullary portion not unlike the mammalian kidney. The cortex extends distinctly beyond limits of the central part of each lobule, this peripheral portion presenting an appearance not unlike that of the reptilian and especially that of the turtle kidney. By use of the above-mentioned methods of maceration and teasing, it may be determined that the more peripherally placed tubules of a renal lobule present an appearance very much like that of the reptilian renal tubule, while those found in the core of the lobule resemble very closely the mammalian renal tubule, with transition forms as one passes from the periphery to the more central portion of the lobule. This is evidenced in the several renal tubules shown in Fig. 4. Tubule *A* of this figure presents a total length of approximately 6.5 mm. It begins in a relatively small, nearly spherical renal corpuscle. The proximal convoluted portion of this tubule having a length of 2.8 mm, is arranged in the form of a left-N

mediate segment is followed by the distal convoluted portion, arranged in the form of a number of compactly placed small loops, from which extends a junctional segment leading to a primary collecting duct. Tubule 1, as shown in Fig. 4 is mounted after

blance in form. The tubule figured in *B* of Fig. 3 presents a length of 13 mm. of which approximately 7.5 mm. fall to the prominent coil complex seen to the left of the figure and representing the proximal convoluted segment. The beginning of a medullary loop is noticed as also a distinct distal convoluted portion. In tubule *C* of Fig. 4 is shown an avian renal tubule teased from the more central portion of a renal lobule and represents a very successful teasing and mounting of the more fully developed avian metanephric tubule. The figure shows the form of this tubule so clearly that little discussion seems necessary. The entire length is approximately 15.5 mm. of which 8.5 mm. fall to the proximal convoluted portion, 3.5 mm. to the medullary loop, 2.2 mm. to the distal convoluted segment and 1.2 mm. to the junctional segment. The tubule begins in a relatively large, nearly spherical renal corpuscle.

**The Metanephric Tubule of Birds**—In the study of the renal tubule of birds use was made of the kidneys of adult chicken *Gallus domesticus*. Use was made of especially devised methods of maceration and teasing. The material was prepared for teasing by injecting the fresh kidney through the renal artery with a 75 per



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scope The kidney of the bird is an elongated, distinctly lobulated organ with the ureter passing on the ventral and meso-ventral side prominent branches passing from the ureter to the several lobules The central portion of each lobule may be divided into a cortical and a medullary portion not unlike the mammalian kidney The cortex extends distinctly beyond limits of the central part of each lobule this peripheral portion presenting an appearance not unlike that of the reptilian and especially that of the turtle kidney By use of the above-mentioned methods of maceration and teasing, it may be determined that the more peripherally placed tubules of a renal lobule present an appearance very much like that of the reptilian renal tubule while those found in the core of the lobule resemble very closely the mammalian renal tubule with transition forms as one passes from the periphery to the more central portion of the lobule This is evidenced in the several renal tubules shown in Fig. 4 Tubule 1 of this figure presents a total length of approximately 6.5 mm It begins in a relatively small nearly spherical renal corpuscle The proximal convoluted portion of this tubule having a length of 3.5 mm is arranged in the form of a letter N each part of the N presenting numerous loops and coils The

mediate segment is followed by the distal convoluted portion arranged in the form of a number of compactly placed small loops from which extends a junctional segment leading to a primary collecting duct. Tubule 4 as shown in Fig. 4 is an example of a

coil complex seen to the left of the figure and representing the proximal convoluted segment The beginning of a medullary loop is noticed as also a distinct distal convoluted portion In tubule C of Fig. 4 is shown an avian renal tubule teased from the more central portion of a renal lobule and represents a very successful teasing and mounting of the more fully developed avian metanephric tubule The figure shows the form of this tubule so clearly that little discussion seems necessary The entire length is approximately 15.5 mm of which 8.5 mm fall to the proximal convoluted portion 3.8 mm to the medullary loop 2.2 mm to the distal convoluted segment and 1.2 mm to the junctional segment The tubule begins in a relatively large nearly spherical renal corpuscle



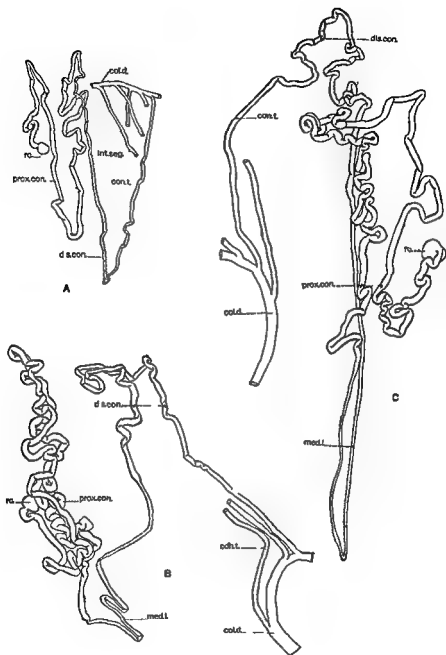


FIG 4—A Metanephric renal tubule of hard *Gallus domestica* completely

The whole tubule in form sequence and relative position of parts resembles very closely a mammalian renal tubule.

A discussion of the form and structure of the pronephric mesonephric and the simpler metanephric renal tubules has been introduced to show that while it must be recognized that one is dealing with a phylogenetically serially arranged excretory renal system which in ontogeny do not differentiate with successive stages of a single organ but with developmental and regressive stages in a series of organs each of which presents excretory tubules and a duct system there is nevertheless a very distinct resemblance both in the form and structure of the renal tubules of the different forms, especially as concerns the mesonephric and the simpler metanephric renal tubules. In a typical renal tubule phylogenetically considered there are to be observed distinct regional cytological differentiations which may be serially enumerated as follows. (a) The renal corpuscle consisting of an arterial capillary net the glomerulus enveloped by a double-walled glomerular capsule with visceral and parietal layer lined by delicate squamous epithelial cells and representing the invaginated end of the renal tubule. (b) the proximal

intermediate segment in the different forms varying greatly in relative length of small diameter and lined by low cuboidal or squamous cells which may or may not support cilia and in position comparable to the medullary loop of the more complex mammalian renal tubule. (c) the distal convoluted segment of variable length and lined with low columnar epithelium with basal cytotreticular striations. Exceptions to the above general statements are found in the nephrostome of the pronephric renal tubule which functionally appears to replace the renal corpuscle and the aglomerular renal tubules found in certain teleosts but even in such forms one may be able to determine with a variable degree of certainty the successive tubular segments with characteristic cytological differentiation as here enumerated.

The consideration of pronephric mesonephric and the simpler metanephric tubules seemed also desirable by reason of the fact that a relatively large per cent of the more recent observations on renal secretion relate to the mesonephros of amphibia. We may cite the outstanding work of Richards and his collaborators<sup>20, 21</sup> who have devised a technique for collecting glomerular urine from a single mesonephric glomerular capsule which has enabled them to compare glomerular urine with simultaneously collected bladder urine and the studies of Marshall and his collaborators<sup>14</sup> on the

functional activity of the glomerular kidney of teleosts which while probably representing phylogenetically and ontogenetically degenerated renal tubules are nevertheless of fundamental importance. The exposed ventral position of the renal corpuscles in the amphibian mesonephros admits of experimental work which it would be quite impossible to carry on even in the metanephric kidneys of reptiles and birds and aglomerular renal tubules are not found in forms having the metanephros.

**The Mammalian Metanephric Tubule**—Our present-day conception of the form, length and relative position of the several parts of the mammalian renal tubule is a composite of observations extending over many decades. The personal names which in the older literature are found attached to different parts of the mammalian renal tubule may serve as an index of the steps through which our knowledge was acquired. We read of the Malpighian corpuscle, Bowman's cap, *la capsule de Bowman*, *capsula* of Henle and the distal

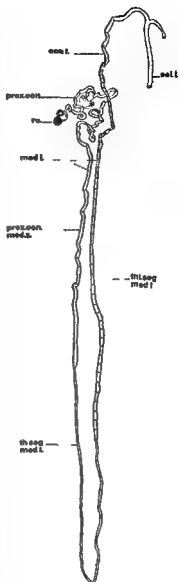
Two methods have been

form of the mammalian renal tubule. (a) The method of wax plate reconstruction especially effective in the study of the developmental and young stages of the renal tubule since in the models made it is possible to reproduce the several parts in their normal relations and (b) especially devised methods of maceration and teasing permitting isolation and mounting in a semipermanent way of completely teased renal tubules of the adult. By such methods of teasing many tubules may be studied and the relations of their several parts determined even though the details of the topographical relations of the several parts may be destroyed as a result of the type form and cytological studies.

tubule we shall base our description on a completely isolated and successfully mounted preparation of the renal tubule of an adult

proximal convoluted portion with the medullary segment, the medullary loop, the distal convoluted portion and the junctional tubule. The mammalian renal corpuscle is of approximately spherical form and varies in diameter between about  $100\ \mu$  to  $200\ \mu$ , its size being roughly correlated with the length of the respective renal tubule. The glomerulus with its afferent and efferent arterial branch and the capillary net will receive discussion when the renal blood supply is considered. The visceral layer of the glomerular capsule surrounds very closely the glomerulus and consists of a single layer of delicate squamous epithelial cells with slightly serrated borders. At the vascular pole of the renal cor

puscle, visceral layer of the glomerular capsule becomes reflected into the parietal layer the epithelial cells of which are of flattened polygonal form and gradually become thicker as the urinary pole of the renal corpuscle is reached. The squamous epithelium of the visceral and parietal layer of the glomerular capsule constitutes a distinctive variety of epithelium in the renal tubule. It is to be postulated that the epithelium of the visceral layer over the glomerulus is deserving of especial consideration in a discussion of the function of the several epithelia of the renal tubule. The renal tubule proper is attached to the renal corpuscle by means of a short neck, an extension of the parietal layer of the glomerular capsule. This continues as the proximal convoluted portion with medullary segment. It forms that portion of the renal tubule presenting the greatest diameter  $30\mu$  to  $10\mu$  loops toward the periphery of the kidney cortex and ends in the peripheral zone of the medulla. This tubule is lined throughout by an epithelium which presents specific cytological structure and is here designated renal epithelium. Irrespective of the total length of the renal tubule which in the rabbit varies from about 20 mm to about 30 mm the length of the proximal convoluted portion is essentially the same in all renal tubules.



approaching a length of 10 mm. The cytological structure of the renal epithelium is not easily determined in that this epithelium quickly shows postmortem changes and appears to present different appearances depending on the fixation and staining methods used.

The structural appearance also seems to vary dependent on the phases of physiological activity. As seen in cross section the tubule of the proximal convoluted portion may present a relatively low epithelium with wide lumen or a high epithelium with relatively narrow lumen with transitional stages. The cells possess relatively large nuclei of spheroidal shape. In the supranuclear portion of the cytoplasm there is to be noted a delicate vertical striation designated as brush border characterizing renal epithelium. The basal or hyponuclear portion of the cytoplasm presents a distinctly striated or rodlike appearance thought to be due to the presence and the arrangement of granules in the cytotreticular threads. Mitochondrial granules have been found distributed in the cytoplasm of the cells of the renal epithelium of the proximal convoluted portions of the renal tubule. In the great majority of the mammalian renal tubules the medullary segment of the proximal convoluted portion extends for a short distance into the periphery of the medulla where the tubule becomes greatly reduced in diameter. Thus the thin segment of the medullary loop presents a diameter which varies from  $20\ \mu$  to  $25\ \mu$  and is of very variable length. It is lined by squamous epithelium the cells having polygonal form and relatively large nuclei and appearing thicker at their center than at their

loop varies greatly

with the relative p

the kidney. In renal tubules having renal corpuscles situated near the periphery of the cortex the thin segment of the medullary loop is relatively short while in renal tubules having renal corpuscles situated in the depth of the cortex near the boundary of the medulla the thin arm of the medullary loop is relatively long with intermediate stages. In the kidney of the adult rabbit the variation of the length of the thin segment of the medullary loop falls between about 1 and 15 mm. In the renal tubule of the rabbit's kidney the thin segment of the medullary loop may be found entirely on the proximal side of the loop may extend into the loop or it may embrace the loop forming a portion of both the proximal and distal arms. This thin arm of the medullary loop is followed by a segment which includes the greater portion of the distal limb of the medullary loop and the distal convoluted portion

either in the proximal  
f or in the distal limb  
varies between  $20\ \mu$   
and  $40\ \mu$  and is lined by a low columnar or cuboidal epithelium

presenting a clear supranuclear zone of cytoplasm devoid of brush border but with basal striation due to the presence of granules in the cytotreticulum though these are not quite so distinct as those found in the renal epithelium. Mitochondrial granules have been found in the cytoplasm of the cells of the distal convoluted portion. The distal convoluted portion joins the primary collecting duct through a junctional tubule with epithelium like that of the collecting ducts. It is evident from this discussion that there are to be found four distinctive epithelial types in a mammalian renal tubule these are (a) The squamous epithelium of the glomerular capsules (b) the renal epithelium of the proximal convoluted portion with the medullary segment with brush border and basal striation (c) the squamous epithelium of the thin segment of the medullary loop and (d) the short columnar or cuboidal cells of the thick segment of the medullary loop and the distal convoluted portion with basal striation but devoid of the brush border.

The primary collecting ducts of the cortex of the kidney either unite in the periphery of the cortex to form collecting tubes which pass through the cortex without receiving further branches or a limited number of primary collecting tubes join in the periphery

dichotomously in two successive divisions so that each forms four collecting ducts of the tenth order each of which passes into the cortex without further division there to branch further and to

1        —        —        "        —        1

Throughout the duct system cells with clear protoplasm and with relatively large nuclei of spherical or ovoid form. The mammalian kidney substance after requisite maceration can be separated into slender pyramidal masses involving both cortex and medulla to which the term pseudolobuli has been given. The apex of such a pseudolobule is formed by a collecting duct of the eighth order. The four unbranching collecting ducts of the tenth order pass through the medullary portion of the pseudolobule and around them and between them are found the medullary loops of the renal tubules collectively constituting a renal pseudolobule. The cortical portion of a pseudolobule continuous with that of the medulla has the form of a truncated pyramid in which the collecting ducts and the straight portions of the renal tubules occupy an axial position surrounded by the convoluted portions of the renal tubules. The renal corpuscles are thus found at the periphery of the cortical

portion of a renal pseudolobule. By reason of the fact that a mammalian renal tubule corresponds to a type form composed of serially arranged tubular segments each having a specific epithelial

lining and consequent differences of diameter and transparency, the kidney substance composed of such renal tubules and especially is this true of the medulla, becomes divisible into zones which have been especially designated by Peter. According to this observer, the medulla is divisible into an outer and inner zone the outer zone being further divisible into an outer and inner stripe. The boundaries of these zones and stripes are dependent on structural changes occurring in the epithelium lining the renal tubules at respective levels. The boundary between the outer and inner stripe of the outer zone lies in the region of change from the thick tubule of the medullary segment of the proximal convoluted portion to the thin segment of the medullary loop and the boundary line between the outer and inner zone falls to the region of the change from the thin segment of the medullary loop to the thicker segment of the thicker distal ascending portion of the medullary loop. The general arrangement of the parts of the renal tubules and ducts of a pseudolobule and the relations of the several parts of the renal tubule to the zones and stripes of the medulla are portrayed in Fig 6. In renal tubules from the kidneys of an adult rabbit completely teased and mounted with renal corpuscles relatively placed as in the three renal tubules shown in Fig 6 namely, periph

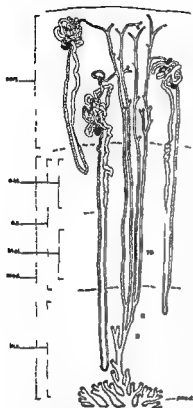


FIG 6.—Diagram of mammalian renal tubules with collecting duct system indicating topographic relations of the different tubular segments and their relations to the medullary zones as given by Peter. Diagram based on reconstructions and teased preparations and refers in the main to human renal tubules: *cort* Cortex *out* outer stripe *in* inner stripe *med* medulla *out* outer stripe *in* inner stripe *pap* papillary ducts terminating in renal calyx. 8, 9 and 10 refer to the respective successive divisions of the collecting tubule including such divisions as are absorbed into the developing renal pelvis. Collecting ducts of the eighth generation form the apices of renal pseudolobules (Huber Cowdry, "Special Cytology" courtesy of Paul B. Hoeber, Inc.)

to the long tubule with the renal corpuscle placed deep in the cortex

TABLE 1

	A mm	B mm	C mm
Proximal convoluted part on with medullary segment	11.3	9.4	10
Distal convoluted part on	1.4	0.7	15.0
Distal convoluted part on	7.8	6.9	3.6
(Cubic or short columnar epithelium)			
Total length of tubules exclusive of collecting duct	20.5	17.0	28.6

The ultimate distribution of the bloodvessels within the kidney and the relations of the terminal capillaries to the renal tubule deserve special consideration since the opinions maintained relative to these conceptions cannot help but influence very materially the views taken with reference to the functional activity of the different parts of the mammalian renal tubule. In the mammalian kidney the renal artery as it enters the renal sinus divides into anterior and posterior branches which on further division enter the renal lobes coursing beneath the cortex in the form of branches designated arcuate arterial branches. From the convex side of these arcuate arteries and at relatively close intervals are given off moderately branching terminal arteries which pass into the cortex as radiate arteries and in course give origin to afferent glomerular branches collectively furnishing a very rich blood

to the renal corpuscles to form glomerular capillary nets. It is a

the vas afferens breaks up into a capillary network as clearly shown in the reconstructions figured by Johnston and distinctly evident in well injected celluloid corrosion preparations. The capillaries of a glomerulus collect to form an arterial efferent glomerulus. The efferent



ing the rate of the blood flow through the glomeruli. The efferent glomerular arteries of the several lower tiers of renal corpuscles divide into long slender arterioles and capillaries which pass into the medulla surrounding the medullary loops of the renal tubules and the collecting ducts and known as *arteriolæ rectæ*. The efferent glomerular branches issuing from the remaining renal corpuscles redivide to form close meshed capillary nets which surround the convoluted portions of the renal tubules and the tubules of the cortical medullary rays. The *arteriolæ rectæ* and the cortical capillaries pass into tributary veins. Therefore essentially all of the blood which in capillary nets surrounds the different parts of the renal tubules is blood which has first passed through the renal corpuscles and during passage has given off water mineral salts and organic constituents to form glomerular urine.

Extensive use has been made of the so-called vital stains in attempting to analyze and determine the process of renal tubule secretion. The fact that the renal epithelium of the proximal convoluted tubule with medullary segment can be stained by use of certain vital stains has been interpreted as indicative of an excretory function of this epithelium. Through methods devised by Richards and his collaborators<sup>20 21 22</sup> and used in obtaining glomerular urine it was found possible to introduce vital stains into the intracapsular space of a renal corpuscle without injuring the glomerulus and later by histological methods determine the presence of the stain in the protoplasm of the cells of the renal epithelium lining the proximal convoluted tubular segment. Accumulating evidence permits the interpretation that the presence of stain in the renal epithelium is not proof of the secretion of said stain through the epithelium since stain introduced into the renal

dilution through the renal corpuscle. Von Mollendorff<sup>4</sup> has given a comprehensive review of the numerous contributions dealing with the excretion of stains and metanephric renal subject. Evidence is :

a resorption of substances which through selective transudation pass through the visceral layer of the glomerular capsule in very great dilution. The substances to be transudated into the renal capsule are thought to preexist in the blood plasma within the glomerular capillaries and it is postulated that they are not transformed in passage through the endothelium and through the epithelial layer of the visceral lamina of the glomerular capsule. The proximal convoluted segment in pronephric mesonephric and metanephric renal tubules forms a conspicuous tubular segment present

ing great similarity in relative length and in epithelial lining, which epithelial lining is constituted by the renal epithelium with brush border and basal striations and experimental evidence warrants the conclusions that in renal tubules with renal corpuscles and glomeruli water, inorganic salts and organic compounds are reabsorbed to a large extent in this tubular segment and that in this way glomerular urine begins to assume the form of bladder urine. A discordant note seems to be introduced by observers who have studied the structure and function of the renal tubules in aglomerular kidneys. Obviously in the renal tubules of such kidneys there cannot be formed glomerular urine and the evidence seems fully to warrant the conclusion that in aglomerular renal tubules the epithelium of the proximal convoluted segment acts as a secretory epithelium. Observations on the functional activity of renal tubules of aglomerular kidneys are of interest and are important but there does not appear evidence that warrants the deduction that renal tubules with renal corpuscles and functional glomeruli function in the same way as do aglomerular renal tubules.

There is at hand indirect evidence that fluid and salts are resorbed during the passage of the urine through the lumen of the thin segment of the medullary loop. As has been noted above the length of this segment varies within wide limits as measured on completely teased renal tubules from the kidney of a rabbit namely from less than 1 to 15 mm. This wide range in the variation of

length would in itself  
indicate functional activity  
in this segment of the  
tubule presents struc-

tural characteristics suggestive of an absorptive function perhaps active in the absorption of threshold substances.

Within the past decade a number of experimental workers have become enticed by the evidence in favor of the filtration and reabsorption theory as giving the most satisfactory explanation of the excretory mechanism of the renal tubule and confirmatory experimental evidence appears to be accumulating although it must be recognized that there is by no means unanimity in this interpretation of the mechanism of renal secretion. Recent observations of Bensley and Steen<sup>2</sup> in which experimental work of Nussbaum<sup>15, 17, 18</sup> and others on renal secretion after ligation of the renal artery in the frog producing a glomerular inactivity gave evidence which warranted ascribing specific secretory activity to the proximal convoluted tubule of the frog. They recognize the formation of

Thus there is still opportunity for further experimental morphological and experimental observations

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## CHAPTER II

### URINE FORMATION IN THE AMPHIBIAN KIDNEY

By A. N. RICHARDS Ph.D. Sc.D. M.D.

#### THE NATURE OF GLOMERULAR FUNCTION

In order to prove that filtration is the sole process responsible for the separation of fluid from the blood in the glomerular capillaries it is necessary to show (1) That the head of blood pressure

If any authentic exceptions to these requirements are encountered we must conclude that another process or processes ( secretion ) must be concerned in the formation of glomerular urine. Evidence on these three points is presented in order.

1 **Glomerular Capillary Pressure** —The first effort to measure glomerular capillary pressure directly of which the author is aware was made by Hill<sup>1</sup> in 1921. He prepared the frog's kidney for direct microscopic observation, squeezed a portion of it between

measured represented the height of the capillary blood pressure and having found it to be somewhat lower than the osmotic pressure of plasma proteins he concluded that the glomerular process is not one of filtration.

The second attack on this problem was made by Hayman.<sup>2</sup> Two observations on the frog's kidney had previously been made which led to the method of direct measurement which he adopted. (1) When a solution of a dye is injected into the intracapsular space the tubule originating from it can be accurately identified in the mass of tissue under observation as the colored solution flows

injecting pipette to measure the pressure just sufficient to arrest

blood flow through a fraction of the glomerular capillaries. This pressure was taken to be equal to the mean pressure within the glomerular capillaries.

The results of more than 150 measurements showed that the average glomerular capillary pressure (20 cm  $H_2O$ ) was about 54 per cent of the average systolic aortic pressure (37 cm  $H_2O$ ). Since the average value of the osmotic pressure of frog's plasma proteins was found by White to be 10 cm  $H_2O$ , it is obvious that Hayman's results pointed to an excess of capillary blood-pressure amply sufficient to permit the filtration of a protein-free fluid through the capillary walls.

A third series of measurements of glomerular capillary pressure was made by White.<sup>27</sup> He studied *Necturus maculosus*, adopting the method used by Hayman. From the 22 experiments included in his first group, 13 can be selected in which the glomerular circulation is reported as fair, good or excellent. Glomerular capillary pressures in these ranged from 10.1 to 26.5 cm  $H_2O$ , average, 16.15. In addition, White measured the colloid osmotic pressure of the plasma from each of his animals and found that it varied from

Hayman  
Hill. The

question  
pressure  
caused retardation of the movements of corpuscles through the glomerular capillaries and implies that the normal capillary pressure must, therefore, be equal to or less than this. He applied the

vessels of the glomerulus were tributary. Surely the least degree of pressure applied to such a surface which was sufficient to increase resistance to flow in these veins and capillaries must have retarded flow through the glomerular vessels proximal to these, because of the relatively vast extent and distensibility of the rest of the frog's vascular system.

In a paper published seven years later, Hill<sup>28</sup> states that the external pressure was applied quickly and that the criterion was momentary checking of glomerular blood flow, that the average of a "very large number of observations" was 8 mm Hg. The purpose of the suddenness of the application was to avoid what he

calls the "banking up" of pressure from the arterial side. If the exact pressure required to collapse the glomerular capillaries could

measured, Hill has given no adequate information on these points.

Another reason for distrust of Hill's results and confidence in those of Hayman and White can be found in a comparison of his estimations of mesenteric capillary pressures in the frog with those of Landis.<sup>11</sup> The method which Landis used is exquisitely simple and direct. It consists in the introduction of the tip of a micropipette directly into the lumen of the capillary studied or into one of its collaterals together with measurement of the pressure at which equilibrium exists between the fluid in the pipette system and the blood in the capillary. The most frequent figure which Landis obtained for capillary pressure in the frog's mesentery was 13 cm H<sub>2</sub>O. Hill's figure was 8 mm Hg—exactly the same as for the glomerular capillaries. The difference between Landis' figure for mesenteric capillaries, 13 cm, and Hayman's figure for glomerular capillaries, 20 cm, is of the order which might be expected by reason of the interposition of the narrow efferent vessel between the glomerular capillary tuft and the intertubular capillaries.

The adequacy of glomerular capillary pressure to permit the filtration of protein-free fluid against the opposing influences of intracapsular pressure and osmotic pressure of plasma proteins seems to me to have been convincingly proved by the work of Hayman and of White.

2 Does separation of fluid from blood in the glomerulus cease when the glomerular capillary pressure sinks below the sum of intracapsular pressure plus osmotic pressure of plasma proteins?

The claim has been made by White<sup>27</sup> that the answer to this question is negative and he has drawn the conclusion that both secretion and filtration are operative in the glomerulus. His experiments are the only ones of which the author is aware in which this question has been directly studied.

He studied the kidney of *Necturus*. In this animal each renal tubule is connected with a nephrostome which opens into the body cavity. After having identified by the dye injection method a glomerulus and tubule appropriate for study, he closed the mouth of the nephrostome by cauterizing it, blocked the proximal tubule at a point distal to its juncture with the nephrostome and then inserted a micropipette into the intracapsular space. Connected with the pipette was an adjustable reservoir of water, and this was raised to such a height that the sum of the intracapsular pressure plus the colloid osmotic pressure of the blood was greater than the

glomerular capillary pressure which had previously been measured. Thus he reduced the effective filtration pressure in the glomerulus to less than zero. He then observed in each of 7 experiments that a small bubble of air introduced as a pressure indicator into a horizontal tube connecting the pipette with the pressure reservoir moved slowly away from the tip of the pipette indicating that fluid was entering the pipette system from the glomerulus.

If this result could be accepted at its face value it would be conclusive proof of the glomerular separation of fluid from the blood as the result of some process which is not filtration. The author has not seen nor has he yet attempted to repeat White's experiments. The number of variables however in this experiment which must be known and controlled seems to him to be greater than White has considered. Before his conclusion is accepted assurance is desirable on such questions as these:

(a) Is it not possible that the permeability of the glomerular membrane is altered at the beginning of the experiment by the interruption of blood flow necessary for determining glomerular capillary pressure and also during the course of the experiment by the retardation of blood flow consequent upon maintained increase in intracapsular pressure?

(b) Is it certain that the tonicity of the salt solution with which the pipette was filled was the same as that of the blood plasma? If it were higher diffusion from blood to capsular contents would give the result which White found.

(c) Is there an hysteresis of the capsule of Bowman and of the other structures which constitute the walls of the closed system with which the pipette is connected which might result in a lag in return to their original tension following the excessive pressures to which they were subjected in the initial steps of the experiment?

(d) Can specific assurance be given on such obvious details as uniformity of caliber of the index tube its precisely horizontal position and absence of temperature inequalities in the system?

The author raises these questions not he thinks because of

to 0.09 c mm per	three
to five-minute intervals	in one
of his experiments	pressed
by a trivial increase in intracapsular pressure (1 mm Hg)	

From these considerations the author believes that a sound conviction of the existence of processes of glomerular secretion cannot at present be based upon White's experiments.\*

\* The results of experiments made by Dr White subsequently have led him to a conclusion similar to this (Am. J. Physiol. 102: 272, 1932).

## 3 Comparisons of the composition of blood plasma and glomerular urine

The first direct information was obtained by Wearn and the author in experiments with frogs.<sup>24</sup> It was qualitative rather than quantitative and so far as it went agreed with the filtration conception. Fluid collected from a renal corpuscle was free from protein its reaction was on the alkaline side of neutrality and it contained urea, sugar, chloride and also the dyes indigo-carmin and phenol red if these were injected into the circulation during the experiment.

Particularly impressive were the findings of sugar and chloride in glomerular fluid for the reason that neither was contained in measurable amounts in the urine which issued from the ureter. The observation provided the strongest evidence in support of reabsorption from the tubule and—more important for our immediate concern—showed that the glomerular process whatever its nature is not one which takes heed of the physiological necessities of the body for retaining sugar and chloride. Later White and Schmitt<sup>25</sup> obtained similar results in a study of the composition of glomerular fluid from *Urocaerus*.

They then ventured to attempt quantitative study of the composition of the glomerular fluid. The project which seemed hopelessly difficult at first has now been carried to a point where some satisfaction is to be derived from the results.

The first study was directed at the chloride content of glomerular fluid.<sup>26</sup> After a long discipline in the rigorous requirements of T. W. Richards' nephelometric method for estimating Cl they believed themselves capable of consistently estimating Cl in amounts of known solutions approximately as minute as the amounts of glomerular fluid with which they were obliged to deal. Seven out of 10 comparisons of frogs' glomerular fluid and plasma indicated that the Cl content of glomerular fluid was significantly higher than that of plasma. This unexpected result was published but as thought that it constituted a final answer to the question which they representing an initial attempt at a difficult problem which they hoped to attack again. Two years later Freeman, Livingston and the author renewed the study.<sup>27</sup> Estimations of Cl were made on glomerular fluid collected from 10 frogs perfused with Ringer's solution and from 20 living frogs. The outcome of the perfusion experiments was not ambiguous. The group of 20 living frog glomerular secretion contained 8 in which the Cl content of glomerular fluid appeared to be significantly higher than that of the plasma. The net result of this second series was indecisive. We were quite uncertain which results represented the truth—the relatively few which might be interpreted as evidence of secretion of chloride



or the majority which pointed to identity of chloride content of the glomerular fluid and plasma. For this reason, and for the reason that they intended a second repetition of the work, these results were not then published.

The second paper which was published on the quantitative aspects of glomerular fluid was by White<sup>28</sup>. He possessed the combination of information and insight which led him to believe that Barger's micromethod for estimation of molecular weights could be successfully applied to the present problem. The method depends upon the fact that when minute droplets of different solutions of the same substance are placed in juxtaposition in a capillary tube, solvent will pass from the less to the more concentrated droplet. White collected blood plasma and glomerular fluid from *Necturus* and introduced droplets of each into capillary tubes, according to the Barger method, measuring the length of the droplets immediately after the preparation of the tubes and again after the lapse of from eighteen to forty hours. In each of 12 experiments he found that the droplet of glomerular fluid increased in length at the expense of the droplet of plasma thus indicating that glomerular fluid is more concentrated than plasma.

At the same time that White's work was in process, Dr A. M. Walker and the author were engaged in attempts to estimate quantitatively the elimination of certain dyes in the glomerular fluid.<sup>9</sup> The author had previously learned that satisfactorily accurate estimations of the concentration of phenol red in dilute solutions could be accomplished with exceedingly minute volumes of fluid provided the color comparisons with known standard solutions were carried out in capillary tubes of the same caliber. Applying this method to glomerular urine collected from frogs' kidneys subjected to aortic perfusion with diluted horse serum to which phenol red had been added, it was found in preliminary experiments that glomerular concentration of the dye was as high as or higher than that in the perfusion fluid whereas when the same serum was filtered through collodion the concentration of phenol red in the filtrate was only 40 per cent of that in the serum, 60 per

the tubules.<sup>9</sup> Experiments designed to test this possibility showed that it was real, hence the procedure was modified to include obstruction of the renal tubules close to the glomerulus before beginning collection of the glomerular urine. When the perfusion experiments with dilute horse serum were repeated with this modification, the concentration of dye in the glomerular fluid was precisely the same as that in an ultrafiltrate from the perfusion fluid

Turning then to living frogs which at the beginning of the experiment had been injected with small doses of phenol red it was found in a series of 14 experiments that glomerular concentration of this dye is the same as that of an ultrafiltrate from the frog's plasma

A few similar experiments in which indigo-carmine was used yielded a similar result

So it is apparent that at a time when White's confidence in the author's chloride results was being strengthened against his expectation by his own work on total molecular concentration the author's confidence in the same results was being shaken by the outcome of his dye experiments

This led to a decision by Walker to study the Barger method as described by White and to apply it to material collected from the frog.<sup>2</sup> Thirty-one collections of glomerular urine were made and compared with plasma in Barger tubes. Subtracting those in which known technical faults had been identified the results were consistent in showing essential identity in concentration of the two fluids. The contradiction between these results on frogs and those of White on *Necturus* seemed to demand that Walker devote himself to the study of glomerular fluid obtained from *Necturus*. Thus he did in 12 experiments with results which consistently confirmed those which he had obtained in frogs

Toward the close of this study by Walker beginnings of another sort were made as a result of the belief by Dr. L. E. Bayliss that he could construct a conductivity cell suited to the measurement of electrical conductivity in very minute volumes of fluid. This was accomplished and with Walker's aid in collecting the glomerular urine and plasma two series of experiments were completed by Bayliss, one on frogs and one on *Necturus*.<sup>1</sup> The outcome of these agreed with the outcome of the molecular concentration experiments by Walker. Twenty-six experiments were made on frogs, 13 of these were regarded as technically perfect. In these the difference in electrical conductivity between glomerular fluid and plasma was found to be of the same order as that encountered between plasma and ultrafiltrates from it. Thirteen other experiments in which one or another minor defect was identified did not alter the conclusion drawn from the first group.

Glomerular fluid from *Necturus* was studied in 15 experiments, 10 of these were regarded as perfect and in these the total electrolyte concentration of the glomerular urine was indistinguishable from that of an ultrafiltrate from plasma.

In recent months Dr. Walker has been occupied with a project which the author has long hoped would be accomplished and in which a beginning was made by Wearn and the author ten years ago, namely, the quantitative estimation of urea in glomerular

fluid<sup>23</sup> An adaptation of the methods of Benedict and of Folin for urea estimation was made which was found to be reasonably accurate for amounts of urea nitrogen of the order of 0.0005 mg. In a few experiments this method was applied to glomerular fluid from frogs. Walker's plans took a different direction. He conceived that it might be possible to measure the concentration of urea in the glomerular fluid by the hypobromite method. He used a capillary tube and of the increase in length of the bubble of air resulting from the nitrogen set free by the hypobromite were the only measurements required.

In order to test the method 177 estimations were made on known urea solutions of various concentrations. In 90 of these the results were within 10 per cent of being correct; in 129 they were within 15 per cent; and in only 9 did the values found differ from the true values by more than 20 per cent. When a curve of averages was made from the entire series it was found to coincide exactly with the curve of known concentrations of the solutions taken.

Forty-four experiments on living frogs were made in which the urea concentration of glomerular urine was compared with that of plasma. In 22 of these the former value was higher; in 22 it was lower. The average of all the glomerular urine values was 1.3 per cent higher than the average of the plasma values; and when the curve of all the plasma urea values is made the dispersion of the glomerular urine urea values from this is such as to indicate identity of urea content of the two fluids.

If a summary be made of the quantitative comparisons which have been described it will be seen that the great majority of the data point to identity of composition of glomerular urine and protein-free plasma both in frogs and Necturus. The comparisons include total molecular concentration, total electrolyte concentration, chloride, urea and injected dyes.

Before deciding that we are justified in adopting even tentatively the conclusion based on the majority of results we must decide whether good reasons exist which justify the setting aside of the divergent minority.

The two divergencies which concern us are to be found among the estimations of total molecular concentration and of Cl. In every one of White's 12 experiments the glomerular fluid appeared to be more concentrated than the plasma; the outcome of Walker's experiments, on the other hand, was that the glomerular fluid was less concentrated than the plasma. The author to suspect that he may have underestimated the opportunities for

evaporation of his samples during the manipulations incident to the measurements and special experiments by Walker on this point show that it is extremely important. For this reason the author feels that Walker's results are the more credible.

Of the higher Cl discrepancy methods yet applied in these experiments that for Cl is most difficult and most beset with opportunity for error. It is to be observed too that divergent Cl results are inconsistent not only with an equal number of other Cl estimations but also with the outcome of Bawls' series of total electrolyte studies and Walker's studies of total molecular concentration. If chloride were actually as highly concentrated in glomerular fluid as it seemed to be in one-half of the experiments it is incredible that striking differences in total concentration should not have been more frequently encountered. Finally it should be remembered that the frog's kidney possesses extraordinary power of preventing excretory loss of Cl from the body and that this power resides in the capacity of the tubule to restore to the blood Cl which has been eliminated in the glomerulus. It is difficult to believe in the absence of unequivocal

the belief that in frogs and *Necturus* the composition of glomerular urine is indistinguishable from that of a protein free filtrate from plasma.\*

The question may properly be raised whether conclusions derived from the study of glomerular functions in the frog's kidney or in

study can determine

The purpose which the experimentation described in the foregoing pages was designed to serve was the acquisition of data which are capable of only one interpretation. It is disappointing to find

that the verdict is not unanimous. On the whole however, in view of the great technical difficulties it may be regarded as satisfactorily so as could have been expected. It coincides with the verdict which has emerged from a great volume of experimental evidence obtained by different methods on different animals—evidence drawn from considerations of the anatomy of the glomerulus, from relations between renal blood pressure and volume of urine formation from the relation between osmotic pressure of blood-plasma and urine formation and from the study of the metabolism of the kidney under differing conditions of urine formation.

### THE REGULATION OF GLOMERULAR FUNCTION

Proceeding from the belief that the facts at present available

factors as most important

1 Glomerular blood-pressure considered in relation to the colloid osmotic pressure of blood plasma and intracapsular pressure, & effective filtration pressure (White)

2 Rate of blood flow through the kidney & rate of renewal of blood in contact with the glomerular endothelium

3 Permeability of the glomerular membranes

4 Extent of filtration surface

A satisfactory account of this subject would include not only an identification of the influences which are capable of affecting each of these factors but an evaluation of the extent to which each may be effective and an exposition of the interrelationships among them. It need scarcely be said that the author can give no such exposition as this. Our knowledge is as yet too fragmentary to justify the attempt. The best we can do is to exhibit evidence which has enabled us to identify the separate operation of these factors and to strive for means of discovering how they may be studied more fruitfully in the future.

1 **Glomerular Blood pressure** Early in the history of experimental study of renal function the gross relationships between  
Ludwig  
Claude  
gave  
entered

to the rule that urine formation varies directly with arterial blood pressure. Anyone who has had experience in the study of vascular changes in various organs by means of the oncometer will agree that the kidney ranks high in its capacity to undergo vasoconstriction

in response to chemical or reflex stimulation of the vasoconstrictor

It was less easy to demonstrate the existence of a vasodilator nerve supply to the kidney. But Bradford showed in 1899 that when the eleventh to the thirteenth dorsal fibers were stimulated by slowly repeated shocks renal vasodilatation occurred. Dilatation of the renal bloodvessels in response to chemical agencies is however very easy to demonstrate e.g. urea glucose NaCl  $\text{NaHCO}_3$   $\text{Na}_2\text{SO}_4$   $\text{NaNO}_3$ , etc. All of the substances which we class as diuretics dilate the vessels of the kidney.

The statements above provide the basis for what may be called gross explanations of changes in urine elimination secondary to, for example as are associated with irritation severe muscular exertion, etc. It has become possible however to enlarge our conceptions of alterations of renal blood

showed that a minute change in the  $\text{CO}_2$  content of alveolar air caused a relatively tremendous increase in the volume of respiration similarly slight changes in the composition of the blood almost too small to be recognized by analytical methods are followed by seemingly disproportionate alterations in urine elimination. Some insight has been gained into the intrarenal mechanisms which by their exquisite sensibility confer upon the kidney the power to adjust with nicety its excretory accomplishment to the excretory demands of the organism which it serves.

The author's interest and the information which has grown out of it proceeded from a single observation made in collaboration with O. H. Plant in 1916 reported before the American Physiological Society in that year but not published in full until 1922.<sup>24</sup> A rabbit's kidney was perfused with his own blood under circumstances which insured constant rate of blood flow regardless of changes in the caliber of the renal bloodvessels. When the renal bloodvessels were constricted either by stimulation of the vaso-

with the rise in renal blood pressure  
was a swelling of the kidney  
taneous vasodilatation  
such as the leg or gut

phenomenon, it was quite clear that the result must have been due to the peculiar arrangement of the bloodvessels in or connected with the Malpighian bodies. In the belief that the efferent vessel was equipped both with muscle fibers and with constrictor nerves, the swelling was explained as the result of constriction of the efferent vessel with consequent distention of the glomerular capillaries proximal to it.

This result constituted the first experimental evidence of which the author is aware in the support of the thought expressed long before by Ludwig, later by Starling and which must have been in the minds of many of those who believed in the filtration doctrine, namely that intraglomerular pressure is susceptible of regulation by changes in the relationship of the caliber of the afferent and efferent vessels.

It was for the purpose of advancing the study of this problem further that we first turned to the kidney of the frog hoping that it might be possible to gain direct microscopic visualization of the changes inferred to take place in the rabbit's kidney. The possibility of microscopic study of the frog's glomeruli was successfully realized<sup>27</sup> and when minute doses of adrenalin were injected into the frog's circulation, it was found by actual measurement that the glomerular tufts increased in size. This was taken to indicate that constriction of the efferent vessel of the glomerulus induced by

pressure under precisely similar conditions and found that minute dosage with adrenalin caused it to increase. His results, therefore, upheld the original conclusion. In one experiment, for example adrenalin caused glomerular capillary pressure to rise from 12 to 21 cm.  $H_2O$ , while aortic pressure changed only from 37 to 40 cm.

Finally an experiment was developed in which the essential elements of the original experiment on the rabbit's kidney were reproduced in the frog with the added item of photography of the glomeruli.<sup>28</sup> The frog's kidney was arranged for perfusion with

it had caused constriction of some part of the vascular system of the kidney. At the same time there was a visible measurable enlargement of the glomerular capillary tuft. This could only have been obtained as a result of increased pressure within the glomerular capillaries which in turn could only have been due to constriction of vessels distal to the glomerular tuft. Adrenalin does

not, by direct action, dilate the glomerular capillaries, it did not, as Sollmann has suggested, dilate the afferent vessels, from the work on the rabbit kidney we knew that constriction of the intertubular capillaries was not responsible for distention of the glomerulus, hence we were forced to conclude that adrenalin had constricted the efferent arterioles.

This succession of experiments showed that increase of pressure in the renal circulation causes corresponding increase in urine

During the progress of the work our thoughts centered upon the possibility of preferential action which might be exerted by a substance upon the efferent as contrasted with the afferent arteriole. If such could be demonstrated we should be able to understand

developed was as follows: It is common belief that the efferent vessel is smaller in diameter than the afferent; if this is so, and if a constrictor agency (chemical or otherwise) acted equally upon both, resistance to blood flow would increase in the smaller (efferent) vessel more than in the larger (afferent), and if intensity of effect on both vessels were not too great might actually increase glomerular capillary pressure. Thus it was reasoned that if a constrictor substance like adrenalin were present in the renal blood stream in *minimal* effective concentration, the only increase in resistance to blood flow would be produced in the efferent vessels, this would lessen the rate of blood flow through the kidney, but at the same time would heighten glomerular capillary pressure and hence increase glomerular urine formation. Experiments were made to test the soundness of this reasoning, first by Plant and the author,<sup>16</sup> later by Mendenhall,<sup>17</sup> and by Livingston.<sup>18</sup> The rabbits were eviscerated to stabilize their renal circulation and arranged to record changes in size of the kidney, rate of blood flow through the kidney and rate of urine flow. In a few experiments with

seemed to show that such a preferential constrictor action on the efferent vessel had been produced, but the number of experiments in which it could actually be demonstrated was too small to be thoroughly convincing.



Another direction which this thought of possible preferential action of substances upon the afferent vessel took was inconsistent with the first. Like the first supposition this latter one has as yet yielded inconclusive experiments but the author is inclined to think it gives prospect of greater fruitfulness if further explored. It concerns the action of substances which dilate the renal blood vessels and produce diuresis.

Pharmacologists have thought for many years that the action of chemical agents upon living tissue could be decreased by the presence of colloid material (demulcent action). Whatever theory is held concerning the nature of glomerular function we may regard it as established that a protein free fluid is separated from the blood in its passage through the glomerular capillaries. This must mean that the concentration of plasma proteins in the blood which flows through the efferent vessels is higher than the concentration of the plasma proteins of the blood which flows through the afferent vessels. Hence if the water of the plasma of the renal blood stream contains a substance in solution which relaxes arterial muscle and if our conception of the demulcent action of colloids is correct it could be supposed that the dilator action of the substance would be greater upon the muscle of the afferent vessels than upon that of the efferent because of the lower concentration of colloids in the blood entering the glomerulus. A few years ago the author made a group of experiments which seemed to give experimental evidence of the truth of this hypothesis. The frog's kidneys were perfused with acacia solutions of two concentrations 3 and 6 per cent. To a portion of each of these was added caffeine 0.1 per cent. The dilator action of caffeine in the weaker solution was greater than its dilator action in the stronger acacia solution. The details of these experiments were never published.

In perfusing the kidneys that following the action the perfusion rate was not restored hence the control level of vascular tone was not the same in the two tests which were compared in each experiment. This was pointed out by Dr H Florey who then proceeded to repeat the experiments on the kidney and to extend them to the systemic vessels as well in the belief that if the thought was correct it *should be demonstrable in any set of blood vessels* which caffeine was capable of dilating. He failed to substantiate the author's earlier results encountering the same difficulty which he had encountered in the restoration of the original vascular tone between the testing of the two solutions. With Dr J A Reisinger the author submitted the question to reexamination. Encouraged by the observations of Krogh and of Drinker that normal serum contains a substance or substances which have the power of preserv-

ing the normal tone and the permeability of perfused vessels, and and guided particularly by Drinker's work solutions were prepared each of which contained 5 per cent of sterile normal horse serum

solution caused perfusion flow to increase to a greater extent and more promptly than when dissolved in the 5 per cent acacia

Possibly it is unwise to call attention to such experiments as these before they have been pushed to a completely satisfying conclusion. It is hoped to do this soon. In the meantime this

substances which the welfare of the body requires to be excreted at the same time retaining those which it cannot afford to lose we

example with the presence in the blood of excess of *harmful* substances is not sufficient to explain the diuresis which rids the blood of such excess. If our ingenuity in experiment is sufficient we shall surely find means by which the kidney is able to accomplish this independently of gross change in the renal circulation and among these means we may expect to find delicate adjustments of glomerular pressure

There is another factor involved in maintenance and adjustment of glomerular capillary pressure which is associated with the filtration of cell free protein free fluid from the blood as it flows through the glomerular capillaries in viscosity. The high viscosity of

afferent. This must form an element in the resistance to exit of blood from the glomerulus and hence in the glomerular capillary pressure. It is an element which must vary with rate of blood flow volume of glomerular filtrate and caliber of vessels and these

are not so sure of this but even if the two vessels are of the same caliber the higher viscosity of blood in the efferent vessel must inevitably produce the same effect as would smaller caliber

**2 Rate of Blood Flow Through the Kidney**—If filtration is the sole process of glomerular separation of fluid from the blood glomerular blood pressure must be the prime physical factor upon which it depends. Renewal of blood however in contact with the filtration surface is essential if filtration is to continue. Since all or nearly all of the renal blood passes through glomerular capillaries the rate of renal blood flow is an expression of rate of renewal of fluid in the filter. Because the colloids of the blood do not pass through the filter the first fluid to be filtered from any portion of blood encounters the least osmotic resistance to its filtration. Each particle of filtrate subsequently formed from that portion encounters greater and greater resistance because of the increasing concentration of non filterable colloids left behind. Stagnation of blood in glomerular capillaries is therefore an impediment rapid flow of blood in aid to the glomerular filtration process.

Despite the probability indicated in the previous section that changes in caliber of the efferent vessel may effect changes in

same direction. When by heightened aortic pressure alone or by dilatation of the renal vessels with maintained aortic pressure the glomerular pressure rises the blood flow increases when by decrease of aortic pressure or by constriction of renal vessels glomerular pressure falls so also does glomerular blood flow. Thus alterations in renal blood flow can commonly be regarded as intensifying the effect of changes in renal blood pressure.

These statements are all inferences. No studies have yet been made in which renal blood pressure has been kept constant in order to study the uncomplicated effects of alterations in renal blood flow. Many experiments have been made in which renal blood flow was measured along with arterial pressure and rate of urine formation. While they have shown that widely different rates of urine formation may be associated with the same rate of blood flow they do not permit us to identify with clarity the share which change in blood flow takes in the production of changes in renal function as a whole much less of any one of its constituent factors.

It will be recalled that one reason for Herdenhain's denial of the validity of the filtration hypothesis was derived from the fact that partial obstruction of the renal vein did not increase urine output. Arguing that such obstruction must increase glomerular capillary pressure he concluded that pressure is not a primary factor in glomerular function but is important only insofar as it is necessary for an adequate blood flow. He conceived the glomerular epithelium to be a secretory structure the functional capacity of which depends upon its state of nutrition this in turn being dependent

upon rapidity of blood flow through the capillaries. We now believe that Heidenhain was wrong if conditions are created in which partial obstruction of the renal vein does not impede blood flow; urine is not decreased; it is increased. In Heidenhain's experiments in addition to the mechanical effects produced by

that the nutrition of the glomerular membrane is dependent upon the rate of blood flow through it — one which it is wise to keep in mind. While we conceive of the membrane as one through which the physical process of filtration occurs, it must be remembered that it is a living membrane and that its properties must vary with the state of vitality of its cells. Data on the relation between changes in its vitality and its properties of permeability are not at hand.

**3 Permeability of the Glomerular Membrane.** On the question of changes in permeability of the glomerular membrane as factors in the regulation of normal glomerular function, the author has no positive information to offer. It may be recalled that brief interruption of the renal circulation causes albumin to appear in the

and Shevky increased glomerular permeability to trypan blue.<sup>20</sup> Attempts have been made to explain in part the diuretic action of caffeine by an effect on glomerular membrane permeability. It was found that diuresis from caffeine outlasts its apparent power to dilate renal vessels, and hence it was argued that the effect could not be ascribed to vascular action, and since evidence that it lessens reabsorption from the tubules is uncertain, recourse was taken to the conception of increased permeability.

The difficulties which stand in the way of actual determinations of the rate of glomerular filtration under constant conditions of blood pressure and blood flow are apparently insuperable. Until such determinations have been made, however, the explanations of diuretic and antidiuretic effects by changes in glomerular permeability, however plausible, will contain unsatisfactory elements of uncertainty.

**4 Extent of Filtration Surfaces.**—Early in the course of the work which Dr. C. F. Schmidt and the author began in 1920 on the glomerular circulation in living frogs, they were struck by the different appearances which different glomeruli presented.<sup>21</sup> One glomerular tuft might show many capillary channels through all of which blood was swiftly flowing; another might seem to consist of only one or two capillary loops through which blood flow was

apt to be sluggish. In some instances one-half of the glomerular tuft appeared constricted and empty of blood the other dilated and filled with blood. Such differences very puzzling at first soon came to be expected and they came to believe that what was being seen represented different physiological states of the glomerular circulation.

At about the same time it was discovered that the number of visible glomeruli in a microscopic field through which blood was flowing at any one moment was variable. By subjecting the kidney to vasoconstrictor influences the number of active glomeruli could be reduced at will likewise by introducing renal vasodilators the number of active glomeruli could be increased.

A third phenomenon was observed in some of the very first successful experiments which were made *in vivo* that blood flow through a glomerulus or a group of glomeruli or even through a capillary loop of a single glomerulus was apt to exhibit irregular variation in its velocity which amounted in many cases to definite intermittence of flow.

This observation of intermittence has been repeated so many times since by so many different persons in the author's laboratory that despite the failure of Tamura<sup>11</sup> and his collaborators to see it in Japanese frogs the author still has faith in the correctness of the observation. Dr H. Okkels of Copenhagen has written that he has observed it in the frogs which he has studied.

These observations led to the inference that not all of the glo-

that the extent of functioning glomerular capillary surface is not really a variable that constriction of renal vessels other things being equal not only lessens glomerular blood pressure and rate of glomerular blood flow but also the extent of glomerular membrane surface accessible to the blood renal vasodilatation on the other hand not only increases glomerular pressure and rate of renewal of blood in contact with glomerular membrane but also increases the accessible glomerular area.

The inclusion of this factor as a physiological means of regulating the degree of glomerular function made it easier to understand how

slight changes in the composition of the blood might cause relatively great change in volume of urine formed

Evidence that this mode of regulation of glomerular function exists in the mammalian kidney was later supplied by Khanolkar,<sup>10</sup> and by Hayman and Starr<sup>7</sup> in the circulation of rabbits, excised water, and in frozen sections

when injected with the dye. By injecting adrenalin or caffeine they were able to vary at will the number of glomeruli through which blood was flowing at any one moment from 5 to 100 per cent of the total

If the conclusion to which these experiments led is correct, an important question arises how the units which do not receive blood escape asphyxial damage. It is well known that interruption of the renal circulation for very short periods is followed by transient albuminuria, attributable to glomerular damage. The answer which Schmidt and the author made to the question was derived from their observations on intermittence. It seemed right to assume that when only a fraction of the total number of glomeruli are being supplied with blood at one time, the individuals which make up this fraction are constantly changing so that no one is deprived of circulation long enough to suffer damage. Langley's work<sup>12</sup> on the small vessels of the frog's web suggested and gave confidence in this view, for he showed that repeated stimulations of the sciatic nerve cause different vessels to respond by constriction. Following Langley's thought, it seemed credible that when a vessel closed because of a constrictor stimulus, influences such as asphyxia of its muscle began to develop which would tend to cause it to relax, and, having relaxed, it would for a time be refractory to the continuing constrictor stimulus.

It must be pointed out that when the capillaries in a single glomerular tuft exhibit alternations in blood flow of the sort described, these are not due to constriction of the capillary loops. They are due either to contraction of the origin of the capillary from the afferent vessel or to contraction of the afferent vessel at the point of its branching from its parent artery or of a similar branching proximal to this. Conclusive proof of the first type of capillary glomerular intermittence was seen in an experiment in which one loop exhibited steady uninterrupted flow, while two other

at the origin of the glomerular capillaries from the afferent arteriole. Similar behavior at the arterial origin of a capillary was described by Tarchanoff and by Landis, and Okkels, having confirmed the observation of Ruyter<sup>29</sup> that the muscular wall of the afferent arteriole exhibits a specialized thickening close to the glomerulus, found that mechanical stimulation at that point produced contraction.<sup>18</sup>

### FUNCTIONS OF THE RENAL TUBULE

**Reabsorption** — There can now be little reasonable doubt of the existence of processes of reabsorption in the renal tubule. When Wearn,<sup>34</sup> for the first time so far as the author knows punctured the capsule of Bowman and withdrew samples of the fluid which was accumulating there, and when upon appropriate test it was found to contain both sugar and Cl, the urine issuing from the ureter containing none the principle of reabsorption was established. Much previous evidence was in existence which had rendered reabsorption justifiably believable but no previous experiment possessed the compelling force of this one.

In one of Hill's<sup>9</sup> papers the objection has been raised that the process which was used to collect the glomerular urine was equivalent to cupping; that the negative pressure employed to draw the fluid up into the pipette produced suction upon the glomerular membrane and that this resulted in the collection of something quite different from the normal glomerular fluid.

that there could be no question of reflux from tubule, and collection of glomerular fluid was made against a positive pressure of 3 to 10 mm Hg. Furthermore almost all of the collections which

tubule closed

At about the same time that the experiments by Wearn and the author were being made Bieter and Hirschfelder<sup>7</sup> injected phenol red into frogs and observed that the contents of the tubules appeared to be more intensely red than did the contents of the capsule of Bowman. This observation was presented as proof of reabsorption of water from the tubule.

There can be no doubt concerning the correctness of this observation, and there is no doubt in the author's mind that water is actually reabsorbed from the tubules but the claim that the observation constitutes proof of water reabsorption seems to beg the disputed question of secretion of phenol red by the tubules.

Other evidence on this point is available.<sup>22</sup> For example, let a frog's kidney be perfused via the renal arteries with a dilute solution

of phenol red in Ringer's fluid long enough to fill the lumina of

diffuse pink to intensely red irregular curved streaks. These streaks can be proved to represent accumulations of the dye within the lumina of the tubules much more highly concentrated than the original fluid. Such concentration could be produced only by the reabsorption of water.

Essentially the same demonstration can be made in a single tubule of the living frog. Inject a minute quantity of phenol red solution into the lumen of a tubule by a pipette thrust into the intracapsular space. Block the neck of the tubule with a glass rod. The injected solution then remains stationary within the tubule and the observer can see that in volume it becomes gradually less while the intensity of its color increases. These experiments are important in furnishing objective evidence not only that water is reabsorbed but also that the highly diffusible substance phenol red is not reabsorbed to the same degree as the reabsorption is selective.

We have a little information concerning the portions of the tubule in which reabsorption occurs. White<sup>22</sup> obtained evidence that the reabsorption of dissolved constituents of the glomerular filtrate takes place in the proximal sections of the tubule. He injected red blood cells into the intracapsular space and found that they became invisible in passing through the proximal convolutions. This he attributed to the reabsorption of chloride to such a degree that hemolysis occurred.

By filling a single tubule with phenol red and then blocking it at different points to learn where the concentration of color became most conspicuous, the author has found that reabsorption of water takes place in an intermediate part of the tubule distal to the proximal convolutions. And if we may regard reabsorption of hydroxyl ions as the cause of the acidity of urine, it can be stated that this occurs in the distal convolutions because phenol red does not turn yellow within the tubule until it reaches the distal convolutions. As yet however there is no direct proof that urinary acidity in the frog is produced by reabsorption of  $\text{OH}^+$ .

These statements are the only ones which the author can make concerning differentiation of reabsorptive function among different parts of the renal tubule.\*

\* occurs only in the distal tubule. Water is reabsorbed from both sections of the tubule more from the distal than from the proximal.



Concerning the nature of the process of reabsorption we have no information other than that it is not to be explained, as Ludwig first conceived by simple diffusion. It must be regarded as active and selective. In experiments on the surviving frog's kidney in which the tubules and the intertubular capillaries are filled with the same solution (Ringer's) chloride and sugar pass from the interior to the exterior of the tubule phenol red does not. The selective reabsorption thus demonstrated and the selective impermeability as well are dependent upon the vitality of the cells of the tubule, for they are not demonstrable in the kidney poisoned with  $HgCl_2$  or damaged by long perfusion. It is proper to think of the reabsorption processes concerned as "secretory" for certainly the activity of cells is a necessary factor in it.

We have scarcely the beginning of knowledge of the factors which control reabsorption from the renal tubule. Clark<sup>3</sup> has shown that the concentration of glucose in the fluid which bathes the tubules determines the elimination of glucose *via* the ureter. C. J. Gamble has found that increase in concentration of Cl in the fluid used to perfuse the renal portal vein stops the reabsorption of Cl from the tubules. Hence we may conclude that the level of concentration of certain urinary constituents in the blood in the intertubular capillaries controls the reabsorption of those substances from the urinary tubule. A. M. Walker showed in perfusion experiments that changes in rapidity of flow of the glomerular filtrate through the tubules may greatly modify the Cl content of the fluid issuing from the ureter. Hence time of contact of glomerular fluid with the tubular epithelium may be looked upon as a controlling factor. Continued search for other controlling factors, nervous and chemical, will surely bring to light more subtle mechanisms than those by which reabsorptive power of renal epithelium is adjusted to the needs of the body.

**Secretion** — Neither the space nor the knowledge at the author's disposal is sufficient to justify an attempt at thorough discussion of the highly involved question of secretion by the renal tubule. Four groups of experiments will be described to indicate the more

<sup>1</sup> + what attempts in which the author has taken part to of view derived from them.

<sup>2</sup> important paper published

by Marshall and Vickers, in 1920. They discovered that when phenol red (phenolsulphonephthalein) is injected into dogs, by far the greater part of the injected dye quickly accumulates in the cells of the convoluted portions of the renal tubules. Then, from estimations of the amount of phenol red eliminated by the kidney in measured time and the concentration of "free" or filterable phenol red in the blood plasma, they computed that the quantity of dye eliminated was greater than the quantity of filterable dye

which had traversed the kidney in the blood stream during that interval. The excess dye eliminated they believed to have been secreted from the deposit previously laid down in tubule cells. Their argument contained two unproved assumptions: one that the glomerular fluid contains phenol red in concentration identical with that of an ultrafiltrate from the plasma. From later work on frogs' kidneys we believe this assumption to be correct. The other was that maximal rate of blood flow through the dog's kidney cannot be greater than 5 cc per gram per hour. This we believe

#### Kidney \*

The outcome of the interest which this paper by Marshall and Vickers aroused was a collaborative effort by Barnwell and the  
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was an exceedingly simple experiment easily performed which seemed to yield *prima facie* evidence of the existence of secretion of phenol red by tubules. The living kidney of a pithed frog was excised, the blood washed out of it by perfusing a little of Ringer's solution through its vessels and then it was immersed in a beaker of thoroughly oxygenated Ringer's solution containing a low concentration of phenol red (0.01 to 0.03 per cent). During the following three to five hours it was taken out of the solution at intervals and examined microscopically. After one half hour and to an increasing degree thereafter the lumina of some of the loops of tubules visible on inspection of the ventral surface were found to be filled with fluid far more intensely colored than was the solution in which the kidney was immersed. Obviously the dye had penetrated into the tubules and was concentrated there; equally obviously the glomeruli could not have participated in the process for no fluid at all had passed through their vessels; the most obvious conclusion was that tubule cells had secreted the dye from the surrounding fluid into their lumina. Further elaboration of the experiment however yielded observations which forced us to think that quite a different explanation was credible.

(a) When the experiment was repeated after the addition of a little HCN to the phenol red solution in which the kidney was immersed no accumulation of the concentrated dye in the tubules occurred but it was easily seen that the dye in low concentration

\* Further experiments by Marshall (Am J Physiol 99:77 1931-32) have established the conclusion drawn by Marshall and Vickers that in dogs glomerular filtrate alone is inadequate to account for the rate of excretion of phenol red.

had penetrated into the tubules. The conclusion was drawn that the vital factor in the original experiment was not the passage of the dye from the outside to the inside of the tubule but rather its concentration within the tubule.

(b) The tubules of a freshly excised kidney were filled with phenol red solution by injection *via* the ureter this was tied to prevent leakage of the injected fluid and the kidney immersed in oxygenated Ringer's solution containing no dye. Immediately after the injection the whole kidney was uniformly pink but after immersion for one hour the dye became localized in precisely similar fashion to that seen in the original experiment i.e. in some of the parts of the tubules visible from the ventral aspect there were accumulations of concentrated dye these being interspersed among areas of relatively little color. When this experiment was repeated with the addition of HCN to the injected dye solution no such localized concentrations of dye occurred. On the contrary the kidney diffusely colored gradually gave up the dye to the fluid in which it was immersed.

From these experiments it is obvious that the fluid with which the tubule of the normal kidney was filled had been set in motion and that at one portion of the tubule water but not phenol red had been extruded (reabsorbed) so that presently that part of the tubule came to contain concentrated dye other parts at the same time becoming relatively empty of dye. The tubule of the HCN kidney on the other hand had lost both its power of extruding water and of retaining phenol red.

(c) Experiments similar to those of the second group just described were made with the colloidal non-diffusible dye vital red. The results were the same except that in the HCN kidney the dye did not leach out into the surrounding fluid but remained for hours diffusely distributed throughout the kidney.

The conclusions which were drawn from this succession of tests were these. When the excised surviving kidney is immersed in oxygenated Ringer's fluid containing phenol red the fluid slowly passes through the wall of the tubule into its lumen as the result of a process which is not inhibited by HCN and hence can be thought of as diffusion rather than secretion at the same time reabsorption processes are operating to extrude water but not phenol red from a portion of the tubule situated distal to the proximal convolutions. (This is the portion most easily seen from the ventral surface.) Both the water extruding and phenol red retaining capacities of this part of the tubule are inhibited by HCN and hence are vital in nature. The simultaneous occurrence of inward diffusion of dilute dye outward extrusion of water and retention of dye within the lumen of the extruding portion results in the accumulation of highly concentrated dye in that portion.

If our reasoning is sound, it is apparent that our original experiment with the excised kidney, which seemed to provide objective evidence of tubular secretion of phenol red, finds a more acceptable explanation in processes of non-selective diffusion into the tubule and selective, active extrusion from the tubule \*

These results are not to be regarded as confirming or not confirming the conclusions which Marshall and Vickers drew from their experiments. They may have value in that they call attention to the possibility that diffusion from blood or lymph into renal tubules may play a part in excretion by the kidney. We have no reason to think it important in the frog's kidney, it is conceivable that it may be a factor of moment in the mammalian kidney, the tubules of which elaborate a fluid highly hypertonic to blood. But methods of studying the question in mammals are not now obvious.

2 The second group of experiments which the author wishes to describe under the general heading of secretion by the renal tubule was the direct outcome of the estimations made by Walker and the author of the concentration of phenol red in glomerular fluid collected while the kidney was excreting that dye. They are analogous to those by Marshall and Vickers described above.

If we know the concentration of some chosen dissolved constituent in the glomerular filtrate, the total number of glomeruli participating in the process of filtration and the total amount of the constituent excreted by the kidney in a measured time, it is obvious that we can compute an average for the rate at which filtration must have proceeded in each glomerulus during that time in order to have effected the clearance from the blood of the amount of the constituent which was actually excreted. In the frog we know

the basis of an opinion concerning the adequacy of glomerular filtration to clear the blood of the amount of the chosen constituent which was actually eliminated and hence, also, of the necessity of postulating secretory functions for the renal tubule.

Walker and the author have made a series of 32 experiments on frogs in which this type of computation of the average rate of glomerular filtration has been made. Phenol red was the constituent of glomerular fluid chosen for study because of the ease with which its concentration in minute amounts of fluid can be determined. The details of one experiment will suffice to illustrate the entire group.

Three milligrams of phenol red were injected subcutaneously

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into a large frog (*Pipiens*). Salt solution was also injected at the beginning of the experiment in order to insure diuresis and active circulation through all the glomeruli. Urine collected from one kidney for thirty minutes measured 0.1 cc and contained 0.1 mg of phenol red. The average concentration of phenol red in the blood plasma during the one-half hour was 9 mg per 100 cc. An ultrafiltrate from the plasma was estimated (on the basis of many actual filtrations of frogs' plasma containing phenol red) to contain approximately 7.5 mg phenol red per 100 cc. The number of glomeruli in the kidney was 1904. From these figures assuming that all of the phenol red was eliminated by the glomeruli the average rate of filtration in each glomerulus must have been 1.36 cmm per hour.

Of the 32 estimations of which the above experiment is one the two highest computed rates of average glomerular elimination were 2.1 and 2.3 cmm per glomerulus per hour. In 16 the figure was less than 1, in 8 between 1 and 1.5, in 6 between 1.5 and 2.

hour. The conclusion drawn from these experiments is that they yield no evidence that the process of glomerular filtration alone

is sufficient to account for all of the elimination of some of his experiments in which the urea content of urine from the ureter were determined. The conclusion was similar, viz. that glomerular function is adequate to account for the urea clearance from the blood.

3. The experiments next to be described related to the behavior of another dye in the kidney, viz. neutral red, and were made in collaboration with Dr. J. A. Reisinger. In a paper from Hober's laboratory Schemmsky<sup>30</sup> published results which seemed to show that this substance is eliminated mainly by the tubules, little if at all by the glomeruli. He subjected frogs' kidneys to perfusion both through the renal arteries and through the renal portal vein. Addition of neutral red to the arterial fluid resulted in the elimination of a small amount of the dye, the concentration in the urine being less than that in the perfusion fluid. Addition to the renal portal perfusion fluid on the other hand was followed by the appearance of the dye in the urine in concentration three to five times greater than that of the perfusion fluid.

Shortly after this Oliver and Shevky<sup>31</sup> and MacKay and Oliver<sup>32</sup> published the results of experiments which confirmed Schemmsky's conclusion and in a very convincing way demon-



taining less than 0.0005 per cent, which could have contained this amount of neutral red was more than 11.4 cc. Assuming the number of glomeruli which were functioning to have been 2000, the average rate for each must have been more than 20 c mm. per hour. The highest figure for rate of glomerular fluid collection which has ever been estimated in our laboratory is 3.5 c mm. per hour. The author finds it exceedingly difficult to believe that a rate of 20 c mm. per glomerulus per hour is ever attained under the conditions of our experiments.

In another experiment the computed average rate of filtration for each glomerulus was 31 c mm. per hour, in still another, 57 c mm. per hour.

From these experiments on neutral red we have been forced to the same conclusion as that reached by Marshall and Vickers, in 1924, from their experiments with phenol red *viz.* that here is a substance the excretion of which cannot be accounted for by glomerular filtration. Because of the relative non-diffusibility of neutral red the

of the theory of secretion by the renal tubule. Scheminsky and Hober believe that the proximal convolutions are the part in which this secretion takes place.

These sentences are written with some misgivings. Certainly until recently the evidence which has been adduced as proof of the existence of secretion has not possessed convincing power, on the other hand, the basis for sound belief in glomerular filtration and in active reabsorption from the tubule has been greatly strengthened. We have yet to learn whether, in the transfer of such a substance as neutral red from the outside to the inside of the tubule, vitality is actively and directly or passively and indirectly concerned, and we have yet to learn whether normal constituents of the urine are eliminated from the blood in the same fashion. We

conclusions to the physiology of a tubule which originates from a glomerulus cannot yet be made with confidence.

Efforts by Reisinger and the author to come closer to direct evidence of the secretion of neutral red by the tubules have thus far failed. For example, the excised kidney experiment described on page 41, which is successful with phenol red, failed completely

in such experiments salt solution is forced through the tubule from ureter to Bowman's capsule with neutral red no color or only the faintest tinge is seen in the fluid taken from the capsule while with phenol red the color is intense. The author has watched the granules of neutral red which appeared to be within tubule cells hoping to see movement or change of size or shape but without success. It seems proper to mention these unsuccessful incomplete and apparently paradoxical observations for the sake of emphasizing how little we know of the processes responsible for the passage of material through the wall of the tubule in either direction. Finally we have a group of experiments to which the author wishes to make allusion though they are still incomplete for the reason that they possess a trace at least of clinical interest. They concern the behavior of the glomeruli and the tubules of the frog during subacute poisoning with  $HgCl_2$ . A dose of 0.3 mg. of this substance in a large frog commonly causes edema and lessened urine output. Examination of the living kidney of such a frog at any time between the first and the seventh day of the poisoning reveals the fact that the glomerular circulation is intensely active in all of the glomeruli which can be seen. Collection of glomerular fluid can be accomplished at rates wholly comparable with normal kidneys. But if phenol red is introduced into the tubule of such kidneys it does not as in the normal remain within it to become concentrated there by reabsorption of water. It diffuses quickly out of the tubule into the intertubular spaces. In experiments specifically designed to test the question it also appears that the power of active reabsorption of water from the tubule is lost. Hence it appears that the damage which  $HgCl_2$  exerts on renal tubules is precisely similar in its physiological consequences to that which  $HCl$  was found to produce. Loss of power of active reabsorption (of water and substances which are normally reabsorbed) and loss of power of selective retention (of phenol red and substances which are normally retained within the tubule for excretion). The decrease in the formation of urine by such a kidney is obviously non selective diffusion of tubule contents back into the blood stream resulting from the osmotic drawing power of blood plasma proteins together with the abolition by the poison of the normal selective impermeability of the tubule wall.

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in some of the lower vertebrates except that segment 3 is absent or replaced by a short tubular segment of small diameter and characteristic ciliated epithelium, which has been designated the intermediate segment. A ciliated neck segment following the renal corpuscle is also present in many of the lower vertebrates.

In Table 2 are collected data on the sizes of the different segments occurring in the renal tubule of vertebrates. The measurements are all in millimeters, the length being given first in each case, the width second. Blank spaces indicate that the segment does not occur in that kidney. The renal tubules of the different classes of vertebrates are presented in Fig. 7 in a schematic manner.

The data for the table and drawing were obtained as follows. For tubule 1 the data of Conel<sup>12</sup> on *Bdellostoma* and Myxine were used. The data for tubule 2 are taken from the observations of Borcea<sup>5</sup> and Nash<sup>10</sup> on the skate (*Raja stebulafors*). For tubule 3 the observations of Nash<sup>10</sup> and DeFrise<sup>17</sup> on the kidney of the sculpin (*Myoxocephalus octodecimspinosus*)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

\* Polward and Mawas<sup>7</sup> describe the nephron of three fresh water teleosts as

TABLE 2—MEASUREMENTS OF SEGMENTS OF RENAL TUBULES OF VERTEBRATES

Num- ber in figure	Class	Species	Renal corpuscle	Neck segment	Proximal convoluted segment	Inter- diate segment	T1 in part of flexible loop	Distal convoluted segment	Initial collecting tubule
1	Cyclostome	Bdellostoma stouti	0.630 × 0.500	0.400 × 0.050	0.75 × 0.350				1.00 × 0.040
2	Elasmobranch	Rana stultiorum*	0.500 × 0.350	0.050 × 0.040	56.00 × 0.120				0.50 × 0.050
3	Teleost	Myoxocephalus octode- cimus; inosus	0.125 × 0.100	0.035 × 0.015	6.06 × 0.055				
4	Teleost	Ameiurus nebulosus	0.098 × 0.080	0.108 × 0.025	1.23 × 0.050	0.07 × 0.090		1.13 × 0.035	0.20 × 0.030
5	Teleost	Opsanus tau			4.27 × 0.070				0.47 × 0.070
6	Amphibian	Rana catesbeiana	0.125 × 0.100	0.100 × 0.030	36.00 × 0.075	0.20 × 0.022		2.50 × 0.030	0.70 × 0.025
7	Reptile	Chrysemys marginata	0.055 × 0.055	0.025 × 0.020	1.40 × 0.063	0.30 × 0.025		1.00 × 0.035	0.50 × 0.030
8	Bird	Gallus domesticus	0.075 × 0.065		3.60 × 0.063	1.20 × 0.030	1.70 × 0.018	2.20 × 0.040	1.00 × 0.038
9	Bird	Gallus domesticus	0.110 × 0.100		7.00 × 0.063		1.28 × 0.014	4.10 × 0.036	1.20 × 0.035
10	Mammal	Lepus cuniculus	0.121 × 0.096		6.90 × 0.036		12.30 × 0.014	5.75 × 0.025	1.00 × 0.020
11	Mammal	Lepus cuniculus	0.133 × 0.102		6.90 × 0.035			4.35 × 0.025	1.00 × 0.020

\* The proximal convoluted segment is intercalated between two other segments which are not represented in other vertebrates. The first of these measured 7.00 × 0.050 and the second 28.00 × 0.050.



not for the entire tubule. As seen in Table 2 the elasmobranch tubule is even longer than a mammalian tubule. Its extraordinary length as compared with that of the tubule of other classes has made it impossible to represent it in full in Fig. 7.

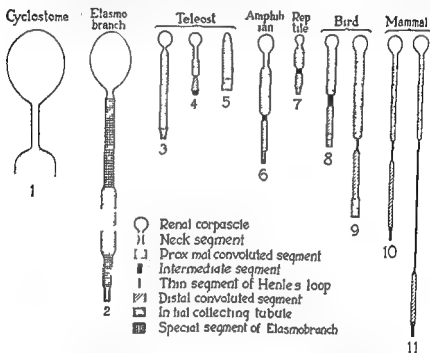


FIG. 7.—Schematic representation of nephron of different vertebrates

It is evident that the proximal convoluted segment as judged by the presence of a brush border ■ the only one occurring in all classes of vertebrates each of the other segments including the

morphological structure offers a method of ascertaining the function of the morphologically distinct parts of the renal unit

**Deductions as to Function**—Certain deductions as to function are suggested by reviewing the structure of the kidney in this way

suggests a relationship of these cilia to the low blood-pressure of the cold-blooded animals. It is probable that in these vertebrates the cilia are needed to aid the relatively low filtration pressure in propelling fluid down the tubule. Again, it seems to be reasonably clear that the ability of the kidney to excrete a urine which is

never hypertonic, compared to the blood plasma (for literature, see Smith<sup>42</sup>), in birds, d'Erincio<sup>41</sup> found that the urine could have a slightly higher osmotic pressure than the plasma and in mammals, as is well known, markedly hypertonic urine can be secreted. Now the thin segment of the loop of Henle appears first in birds, but is completely evolved only in mammals. Indeed, Peter<sup>43</sup> has correlated the length of this segment in different mammals with the ability of their kidney to excrete a more or less concentrated urine.

It is interesting to note that in the schematic representation of the tubules of vertebrates the proximal convoluted segment with

concerned in some way with the urea excretion, since the elimination of a urine with a much lower content of urea than the plasma is a characteristic of this sub-class. (Clarke and Smith<sup>44</sup> have recently shown that in the dogfish the filtered urea may be almost completely reabsorbed by the tubule.)

In view of the fact that more knowledge about the morphology and cytology of the renal tubule in many of the lower vertebrates is needed and that functional studies of many types are almost completely lacking as yet, this discussion must be limited to certain features of the comparative physiology of the kidney.

**The Aglomerular Kidney**—The aglomerular kidney was discovered in the Lophobranchs by Huot,<sup>45</sup> in 1897, and described by him in 1902<sup>46</sup>. In 1910, Audigé<sup>47</sup> in a general study of the kidney in teleostean fish found in the kidney of the goosefish (*Lophius piscatorius*) neither an arterial supply of blood nor glomeruli. The aglomerular nature of the kidney in the Lophobranchs has also been confirmed by Verne<sup>48</sup> and Edwards<sup>49</sup>. The kidney of the goosefish has recently been carefully studied by Marshall and Grafflin<sup>50</sup> and by Edwards,<sup>51</sup> and the common toadfish (*Opsanus tau*) has also been found to have an aglomerular kidney (Marshall<sup>52</sup>). The goosefish and the toadfish kidneys will serve as types for a description of this form of teleostean kidney.

Contrary to the statements of Audigé,<sup>2</sup> it has been found that the kidney of the goosfish has a small arterial blood supply and a very few structures resembling renal corpuscles. Definite renal arteries however, are absent, the main arterial supply being from minute branches of the lateral and ureteral arteries. The main blood supply is almost entirely venous, the afferent venous trunks being the caudal, caudal accessory, sub-clavian and epibranchial veins. The whole kidney can be injected from any one of the afferent veins. The large posterior cardinal vein is the only efferent vessel. Seventy-eight structures resembling glomeruli were found in one kidney, while an estimate of the number of tubules gave about 150 000 as a minimum, or about 1 pseudoglomerulus to each 2000 tubules. Grafflin<sup>24</sup> has shown conclusively that in the adult fish these pseudoglomeruli are non-functional, as careful study by incision and serial section method<sup>25</sup> reveals no connection of these structures with a renal tubule. However, in the kidney of a young fish (63 mm long), he found 94 glomeruli, all of which were connected to renal tubules. It is, indeed, interesting that these glomeruli should lose their connections with the tubules in the adult fish.

The kidney of the goosfish is composed of great numbers of irregularly convoluted tubules with definite blind endings, surrounded by a mass of pseudolymphoid tissue. The tubules may attain a length of 10 mm or more, and have an average diameter as measured in section, of about 0.05 mm. Complete vascular injection of a kidney demonstrates freely anastomosing venous channels closely investing the outside of the tubules. The epithelium of the tubule is described by Audigé<sup>2</sup> as possessing a brush border throughout (with the exception of the initial collecting tubule). Edwards<sup>18</sup> gives drawings illustrating two segments, with and without brush border (proximal and distal convoluted tubule) but subsequently, writing of the distal convoluted tubule, he says "This convolution is present and of considerable length in the kidneys of representative animals in the chief classes of vertebrates except in that of the marine fish" (Edwards<sup>20</sup>). This agrees with Audigé and makes the goosfish tubule an unisegmental nephron.

The kidney of the toadfish is entirely aglomerular, no structures in the least resembling glomeruli are present. This kidney possesses a very small arterial supply, but the main afferent channels are venous. The tubules resemble those of the goosfish and are surrounded by pseudolymphoid tissue. Excluding the initial collecting tubule, it is here certain that only one type of epithelium is present, that of the proximal convoluted segment with brush border.

the whole function of the kidney here is performed by a single type of the proximal convoluted

having a large number of glomerular structures but showing complete lack of glomerular function by physiological tests has recently been explained by Grafflin<sup>4</sup> In the kidney of the daddy sculpin (*Myoxocephalus*

which from careful anatomical study can be considered functional

Comparison III Function of Glomerular and Aglomerular Kidney —

certain marine teleosts but is normally much less than that from the well glomerularized kidney of a fresh water fish Under as nearly normal conditions as can be experimentally attained the urine flow of the toadfish is usually below 2.5 cc per kilogram per twenty-four hours while that of the sculpin (a glomerular marine teleost) may be slightly higher (4 cc or less) How fundamental such a difference is cannot be stated at the present time (Grafflin<sup>4</sup>) The fresh water catfish on the other hand may have a urine flow of over 300 cc per kilogram per day

The urine of both aglomerular and glomerular marine teleosts contains large amounts of magnesium and sulphate very small amounts of urea and relatively large amounts of creatine and

the glomerular kidney is seen also in the case of the aglomerular kidney Thus the urine of the toadfish may contain under some circumstances about the same concentration of chloride as the plasma while under normal conditions it is free of chloride with large amounts of course still present in the plasma It would appear then that the aglomerular tubule and indeed the single segment with brush border can excrete a urine of the same composition as that eliminated by the glomerulus and tubule together

What then are the functional differences of the glomerular and

\* Grollin and fin is that the undetermined nitrogen of goosefish urine is mainly trimethylamine oxide and may constitute .8 to 1.1 per cent of the total nitrogen Hoppe Seyler<sup>2</sup> finds trimethylamine oxide in the urine of selachians but not in that of fresh water teleosts

aglomerular tubule? The inability of the aglomerular kidney to eliminate glucose and other sugars its specificity in the excretion of foreign substances and its ability to secrete against a higher pressure than the blood pressure are the important differences known at present. A rise of blood glucose to over 500 mg per 100 cc is not followed by the appearance of glucose in the urine of the aglomerular fish while a much less degree of hyperglycemia produces glycosuria in glomerular fish (sculpin eel flounder and dogfish). Neither after the administration of phlorizin alone nor in combination with large amounts of glucose can a qualitative test for sugar be obtained in the urine of aglomerular fish. A quantitative investigation of the true glucose in urine has shown that in the urine of the aglomerular fish only traces at most of glucose are ever present.

It appears that none of the sugars are secreted by the aglomerular kidney. Thus Jolliffe<sup>33</sup> and Clarke and Smith<sup>11</sup> have shown that glucose and sucrose although freely excreted by glomerular fish are not secreted by aglomerular fish from plasma levels of 300 to 400 mg per cent. Lactose is not secreted when injected in large amounts into the toadfish.

The glomerular kidney appears to excrete to some extent at least practically all diffusible foreign bodies which may be introduced into the organism such behavior is indeed demanded by the filtration theory of glomerular function. This behavior in regard to foreign substances is not exhibited by the aglomerular kidney the tubule shows specificity in its behavior to these substances just as the so-called true secretory glands do. A study of the excretion of phenol red and ferrocyanide as two distinct types of foreign substances has been made in representative species of the various classes of vertebrates. While phenol red is readily excreted by the kidney of all vertebrates ferrocyanide fails to be secreted by aglomerular kidneys. The concentration of phenol red in the urine of the toadfish may be 150 times greater than in the blood plasma but ferrocyanide when present in the plasma in large amounts can be found in the urine in only faint traces. Phenol red and ferrocyanide are here taken only as types of foreign substances many others could be used. Creatinine uric acid iodides nitrates thiosulphates sulphocyanides indigo carmine and neutral red are all secreted by the aglomerular kidney while iron salts and cyanol are not excreted. Marshall and Grafflin<sup>4</sup> found that injected inorganic phosphate is not secreted by the aglomerular kidney but that the urine from an aglomerular fish may at times contain large amounts of inorganic phosphate. This paradox is as yet unexplained. Bieter<sup>4</sup> has also

that after an intravenous injection of a mixture of phenol red and cyanol into the goosefish the former only is excreted in the urine. He had previously found that phenol red is secreted by the tubule of the frog's kidney and that cyanol is not.

Recently Bieter<sup>1</sup> showed that in the aglomerular kidney (toad fish) the secretion pressure taken in the ureter may be greater than the dorsal aortic blood pressure. Since the main blood supply to the toadfish kidney is venous it appears that the secretion pressure can be many times as high as the blood pressure in the kidney.

through the glomerulus must occur.

**Function of Proximal Convoluted Segment of Renal Tubule —** These studies on the aglomerular kidney of fish and a comparison of its function with that of the glomerular kidney of the same order of animal prove conclusively that the tubule can secrete. The absence of the excretion of glucose and other sugars, the specificity in the excretion of foreign substances and the ability to secrete against pressure establish the excretion of the aglomerular kidney as being a case of *true secretion*. Since the tubule of the toadfish consists of only one segment (Grafflin<sup>24</sup> DeFrise<sup>17</sup>) it is obvious

of the sculpin (Fig. 7 S) has shown that in this glomerular fish the proximal convoluted segment can both secrete and reabsorb (Marshall and Grafflin<sup>25</sup>). The sculpin kidney can be rendered functionally aglomerular by several injections of phlorizin; after such injections it no longer excretes substances which are not secreted by the aglomerular kidney.

This would appear to raise the question: if the proximal convoluted segment is active in secretion, are the glomeruli active? The urine/plasma ratio for glucose after small doses of phlorizin used as a measure of the amount of glomerular filtrate shows that in the marine teleost kidney a large percentage of the magnesium and sulphate of the urine as well as of injected creatinine and phenol red appear to be excreted by tubular secretion.

Since the urine of a normal sculpin is free of chloride and glucose while the plasma contains these substances it follows as a corollary of glomerular filtration that these substances must be reabsorbed by the proximal segment. Reabsorption of water by the proximal segment is proved by the fact that the urine/plasma ratios for glu-

cose and xlose can reach values over 2 (neither of these substances is secreted by the tubule of the sculpin) \* By direct methods White and Schmitt<sup>21</sup> had previously localized the reabsorption of chloride and glucose by the proximal segment of *Necturus*

**Primitive Function of the Glomerulus and Adaptation of Glomerular Development in Animals to Habitat**—Sixteen species of fish belonging to six families are now known to have aglomerular kidneys (Marshall<sup>44</sup>) These all belong to the group of marine teleosts Why do these fish have aglomerular kidneys? This question may possibly be answered by some important work of Homer W. Smith Smith<sup>45</sup> finds that in teleosts about 6 to 10 times as much nitrogen is excreted by the gills as by the kidneys Moreover, he<sup>46</sup> has found that marine teleosts swallow sea water, absorb from the intestine a large amount of the water and salts and excrete by means of the gills a much greater percentage of this water and certain salts than is eliminated by the kidneys † Fresh-water teleosts, on the other hand, absorb water from their environment probably by way of the gills and excrete large quantities by way of the kidney On the basis of this work Smith has suggested that the aglomerular state of certain marine teleosts is due to their peculiar water cycle resulting in the excretion of only small amounts of water by way of the kidney ‡ If this view is correct, glomerular development should be related to the need for water excretion by the vertebrates generally and a preliminary survey of the vertebrate kidney has been made from this standpoint (Marshall and Smith<sup>47</sup>)

The general theory which has been developed may be briefly outlined as follows The excretory organ or kidney of the proto-vertebrate ancestor of the fish was presumably aglomerular, § and in the course of the evolution

was developed in response

taken up in large amounts

these animals lived With a migration to the sea, the need for the glomerulus ceased because water was no longer being taken into the organism in large amount and because the gills could excrete considerable water, due to the difference in the external medium to which they were now subjected Hence the kidney of the marine

\* Marshall and Graffius<sup>48</sup> concluded that the same histological type of cell could both excrete and reabsorb

† and water by the perfused gills of the eel in sea water Keys and Wallmer<sup>49</sup>

toadfish never develops glomeruli is interesting in this connection

§ Nussbaum<sup>50</sup> and Armstrong<sup>51</sup> present definite evidence for secretion in the aglomerular pronephric tubule of fish embryos

has no need for glomeruli unless a new purpose is served by them. The same holds true for the birds and mammals.

If we examine the character of the glomerular development in the different groups of vertebrates, we find that it agrees fairly well with the above hypothesis.

ment of glomerular surface

noans, amphibians and mam-

teleosts, reptiles and birds it is unusually poor. If we adopt a subsidiary hypothesis that in the mammals (and to some extent in the lower vertebrates) the primitive water-excreting function of the glomerulus has been secondarily diverted to the excretion of waste products, we see that the known facts agree well with the hypothesis.

**Relation of Comparative Data to Theories of Urine Secretion** — Let us now see what bearing these fragmentary observations on the comparative physiology of the kidney have upon current theories of urinary secretion. The ability of the glomerular kidney to eliminate to some extent practically all soluble and diffusible substances which may enter the blood stream, and the necessity of the glomerulus for such a process argues for the filtration theory of glomerular function. The abundant other evidence for filtration warrants the acceptance of this theory, with the reservation that possibly the glomerulus may at certain stages of development secrete as well. The high cubical epithelial cells of the visceral layer of Bowman's capsule seen at one stage in the embryonic kidney, the cubical epithelium in certain renal corpuscles of the opossum's kidney described by MacNider,<sup>43</sup> similar findings in the kidney of the mouse (Standfuss<sup>44</sup>) and the frequency with which rather high epithelium on the visceral layer of the capsule occurs

indeed, in the proximal segment. That this same proximal convoluted segment with brush border can also transfer substances from the blood and lymph to the lumen of the tubule is proven by a consideration of the morphological and functional studies on the toadfish kidney which have been outlined. The occurrence of this proximal convoluted segment with brush border in the kidney

\* Osawa<sup>45</sup> states that in the kidney of *Sphenodon* the visceral layer of Bowman's capsule is composed of high cubical cells.



Certain calculations in regard to glomerular filtration in the fowl's kidney may be of interest. The total numbers of glomeruli in the fowl's kidney were found to be 414,000, which compares favorably with data for a rabbit of about the same size. A 2400-gm rabbit was found to have 414,000 glomeruli in both kidneys, the average diameter of the renal corpuscles was  $142 \mu$ . Thus, the glomeruli in the fowl are about twice as numerous as in the rabbit and of about one-half the size. Hence, allowing for the much less developed vascular tuft in the fowl, it is certain that the total glomerular surface of the chicken is considerably less than that of a rabbit of the same weight. But, on the theory that glomerular filtration furnishes all of the constituents of the fowl's urine, difficulties are encountered. A calculation from the urea ratio of Addis (Taylor, Drury and Addis<sup>49</sup>) shows that about 250 cc of glomerular filtrate per hour is required in a 2500-gm rabbit to account for the urea eliminated in the urine, about 300 to 350 cc of filtrate would be required to account for the excretion of creatinine (MacKay<sup>4</sup>). In the case of fowl the figures on uric acid in the plasma and urine require from 1400 to 3300 cc of glomerular filtrate per hour to explain the uric acid elimination on the filtration-reabsorption hypothesis alone. In other words about ten times as much filtration is demanded from the filtering surface in the bird, which is much less extensive than that in the rabbit. It is doubtful if differences in blood-pressure or colloid osmotic pressure could increase the filtration to this extent, especially as the visceral epithelium of Bowman's capsule in the chicken appears to be much thicker than the same structure in the rabbit.

The situation in the arid reptiles, such as snakes and lizards, is apparently very similar to that in the birds, but practically no functional studies have been made of the reptilian kidney.† Here, the small renal corpuscles are poorly vascularized, and hence the total glomerular surface must be small. A comparison may be made of the relative extent of glomerular surface in the horned toad (*Phrynosoma cornutum*) and the common frog (*Rana pipiens*). Hayman<sup>50</sup> has reported glomerular counts on the kidney of the frog of 1592 to 5260 per kidney, the number most frequently being around 2000. Since the size and weight of the frogs is not given,

in both kidneys

† Bordley and Richards<sup>51</sup> report that the analysis of glomerular fluid taken from the renal corpuscles of snakes shows the uric acid concentration to be of the same order as in the blood plasma.

we cannot tell to what extent this factor accounts for the variable counts. We find a 19.5-gm frog to have 1608 glomeruli, a 26.5-gm frog, 2220, a 293-gm bullfrog, 6400, and a 268-gm animal, 8150. We conclude that large frogs have in general a greater number of glomeruli than small ones, and that for frogs of 20 to 25 gm the number of glomeruli per kidney is about 2000. Four horned toads, varying in weight from 16.9 to 24 gm had 1575 to 2425 glomeruli per kidney. It is thus obvious that the kidney of the horned toad does not contain more glomeruli than that of a frog of the same

weight. In the case of the horned toad, however, because of its poor capillary development, it is clear that the glomerular surface in the latter animal is much less than in the former. The total capillary surface of a glomerulus can be taken to vary as its volume if it is entirely filled with capillaries of the same diameter. But the frog's glomerulus is more vascular than that of the horned toad so this assumption gives too high a value for the capillary surface of the latter. Even on this basis, we find that the total glomerular surface of the horned toad is only about 7 per cent that of a frog of the same size.

An arid-living lizard (*Iguana iguana* Shaw) has recently been investigated. The number of glomeruli in the kidney appears to

be much reduced. A comparison of the amount of glomerular filtrate, as measured by the glucose ratio after phlorizin with the amount of uric acid excreted indicates that in the reptiles as in the birds, the major portion of the uric acid is excreted by tubular secretion (Marshall<sup>46</sup>).

In the mammals we find excellent glomerular development. This, together with the complete development of the loop of Henle, suggests that the primitive water-excreting function of the glomerulus has been almost completely modified and the glomerulus now serves as the main route for the excretion of the normal constituents of the urine.\* This agrees with the idea that, in mammals filtration and reabsorption play a major part in the excretion of urine, and that secretion exists only as a relic of a primitive process (Mavrs,<sup>47</sup> Marshall<sup>48</sup>). To explain the formation of hippuric acid and ammonia by the mammalian kidney would seem to necessitate secretion by the tubule, and certain other substances also appear to be secreted

\* Smith<sup>49</sup> has pointed out that the filtration-reabsorption mechanism in the mammal does not owe its existence to any superiority of this method over tubular secretion but is a consequence of the evolutionary history of the vertebrates.

From the work of Jolliffe, Shannon and Smith<sup>17</sup> on the use of non metabolized sugars to measure the glomerular filtrate in mammals it is probable that the filtration-reabsorption mechanism is sufficient to excrete practically all of the normal constituents of the urine. On the other hand, there is now proof that a very large percentage of certain substances is excreted by tubular secretion in the mammal. It is certain that a large amount of phenol red is excreted by tubular secretion in the dog (Marshall<sup>44</sup>) \*. Using xylose as a measure of the glomerular filtrate, Shannon, Jolliffe and Smith<sup>11</sup> have shown that nearly 50 per cent of ingested creatinine may be excreted by tubular secretion in the dog, and Jolliffe and Chasis<sup>36</sup> find that in the human subject about 42 per cent of ingested creatinine is secreted.

Since the evidence is becoming very strong indeed that glucose after phlorizin or xylose can be used to measure the glomerular filtrate in different classes of vertebrates (Jolliffe, Shannon and Smith<sup>17</sup> Clarke and Smith<sup>11</sup> Marshall<sup>44</sup>) † we can give a preliminary table of magnitude of the glomerular filtrate in different animals

all certain that weight or surface area is the proper basis on which to compare different classes of animals. The conditions under which the data for calculation of the filtrate have been obtained are not comparable for all the animals and, since Shannon, Jolliffe and Smith<sup>11</sup> have shown that diet can alter the glomerular filtrate in the dog more than 300 per cent it is obvious that quantitative comparison of the present figures is not justified. Nevertheless, Table 3 does emphasize some of the points which have been dis-

\* Doctor Shannon informs me that by the use of xylose to measure the glomerular filtrate in the dog he has found that a large percentage of the total phenol red excreted from low plasma concentrations cannot be accounted for by glomerular filtration alone. Chambers and Kempton<sup>18</sup> have developed an ingenious method of studying renal function by the use of tissue cultures and a micro manipu-

an agreement as was reported by Jolliffe, Shannon and Smith<sup>17</sup>. Prof Homer W. Smith on the other hand informs me that he and his co workers have accumulated considerable additional evidence of the validity of the use of xylose or sucrose to measure the glomerular filtrate both in the dog and in the human subject. Pitts has recently found that when the plasma level of inorganic phosphate is raised by injection the concentration ratios of inorganic phosphate and xylose approach one

TABLE 3 -- URINE FLOW WATER REABSORPTION AND GLOMERULAR FILTRATE

	Urine flow	U/P ratio glucose or xylose	Glomerular filtrate	Remarks
	cc per k lo per hour		cc per k lo per hour	
<i>Elasmobranch Squalus acanthias</i> (dogfish)	0 19- 1 6	2 15- 6 71	1 21- 4 06	From Clarke and Smith <sup>1</sup> Xylose
<i>Teleost Myoxocephalus octodecemspinosus</i> (sculpin marine)	0 11- 0 9	0 51- 2 75	0 13- 0 06	From Marshall and Graffin <sup>11</sup> Glucose after phlorizin
<i>Ameiurus nebulosus</i> (catfish fresh water)	6 4- 13 6	1 25- 1 90	10 0- 17 3	From unpub- lished observa- tions Xylose
<i>Amphibian Rana ca- sabiana</i>	1 5-20 7	1 16- 3 00	2 8-40 0	From Marshall <sup>11</sup> Xylose
<i>Reptile Iguana iguana</i>	0 20- 1 23	1 5- 4 9	0 3- 3 8	From Marshall <sup>11</sup> Urethane glu- cose after phlo- rizin
<i>Alligator mississippi- ensis</i>	0 43- 1 0	2 6- 4 2	1 5- 3 4	From Burgess Harvey and Marshall <sup>11</sup> Wa- ter diuretic xylose
<i>Bird Chicken</i>	2 8- 7 5	4 7-17 3	25 5- 91 6	From Marshall <sup>11</sup> Urethane glu- cose after phlo- rizin
<i>Chicken</i>	2 0-17 7	5 2- 18 0	36 6-93 0	From Burgess Harvey and Marshall <sup>11</sup> Wa- ter diuretic and pituitary ex- tract Xylose
<i>Mammal Dog</i>	2 7-19 3	7 3-63 2	9- -327	From Jolliffe Shannon and Smith <sup>1</sup> Wa- ter diuretic xy- lose and raffi- nose

cussed above. The very low values for the urine flow and glomerular filtrate of the marine teleosts and reptiles stand in contrast to the high flow and high filtration rate in the amphibians and fresh water teleosts for all animals below poor water-reabsorption ratios, beginning in the bird and reaching its maximum in certain

mammals shows the importance of the loop of Henle for efficient tubular reabsorption of water. Of course in non-diuretic dogs the glucose or xylose ratio can reach very much higher values than those given in the table.

**Blood Supply of Kidney**—A consideration of the blood supply to the kidney of different classes of vertebrates appears to confirm the ideas expressed above. In the aglomerular kidney of the marine

of the Cyclostomes) below the mammals\* there exists a double blood supply to the tubule: an efferent glomerular vessel and a renal portal system (Jourdain<sup>38</sup>, Noll<sup>39</sup>, Spinner<sup>43</sup>). This is quite to be expected if tubular secretion plays a greater role in the lower vertebrates than in the mammals. It is generally believed that the bloods of the efferent glomerular vessel and of the renal portal system mix freely and supply all parts of the tubule, but the functional investigations of Scheminzi<sup>40</sup> and Oliver and Shevky<sup>41</sup> seem to show that this idea of the blood supply of the tubule of the frog's kidney may have to be modified. Their findings indicate that the distal convoluted segment is supplied by the efferent glomerular vessels and the proximal convoluted segment by branches of the renal portal vein. Polcard<sup>42</sup> states on anatomical grounds that this is the case. A more complete and careful investigation of this point should be made.

**Histological Evidences of Secretion**—Many observers have described what they believe to be histological evidences of secretion in the renal cells of the lower vertebrates. Thus rather definite granules or globules of material are described as in the process of extrusion from the cells of the tubule and mesonephric duct of *Myxine* (Conel<sup>19</sup>) and recently Herring<sup>17</sup> has reported what he regards as histological evidence of secretion in the kidney of the skate. Deprise<sup>17</sup> and Oliver and Lund<sup>52</sup> are the most recent writers to present cytological changes in the renal epithelial cells of the lower vertebrates which they believe to be indicative of secretion. The histological evidence for secretion in the cells of the sexual segment of the kidney of male snakes and lizards (Regaud and Polcard<sup>11</sup>, Cordier<sup>19</sup>) and in the renal cells of nest building fish like the stickleback (Hess<sup>24</sup>) would seem to be quite definite.

In conclusion it may be stated that this fragmentary account of certain phases of the comparative physiology of the vertebrate kidney appears to indicate the value of pursuing this line of inquiry to obtain an understanding of renal function from a broad biological

\* Das<sup>4</sup> states that the bird has no true renal portal system similar to that of fishes, amphibians and reptiles.

viewpoint and to evaluate properly much of the work on the lower animals in its relation to renal function in man. From what has been presented we conclude that glomerular filtration, tubular reabsorption and tubular secretion all probably occur to some extent in all vertebrate kidneys (except the aglomerular kidney). The relative importance of the filtration-reabsorption mechanism and of tubular secretion of any given substance depends on the substance in question, the particular species of animal under consideration and the conditions under which the animal is kept. In normal urinary constituents it is possible that under certain pathological conditions the more primitive secretory process in the tubule may be of major importance.\*

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\* This same idea is implied by MacNider<sup>10</sup> who states that future studies of the details of the circulation in the pathological kidney may alter the conception that an obliteration of glomerular vessels results in atrophy of the tubule. Dr. MacNider informs me by a personal communication that he has very definite reasons to believe that under certain pathological conditions a blood supply is furnished the tubular tissue of the kidney independent of the glomeruli.

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## CHAPTER IV

# THE FILTRATION-REABSORPTION THEORY OF KIDNEY FUNCTION AND ITS USE IN THE CLINIC

BY POUL BRANDT RICHBERG PH.D.

**Introduction** — Since Cushing wrote his monograph on the secretion of the urine the filtration-reabsorption theory has been the point around which the discussion of this question has largely centered. Most of the adherents of the old secretion theory have more or less adopted parts of this later theory and fitted it into the older one. Very few now hold that the excretion of urine is a process of purely secretory character, that is, that both glomeruli and tubules secrete. It is a widely accepted view that the process going on in the glomeruli is an ultrafiltration, and it is also widely accepted that substances are reabsorbed again from the filtrate by the tubules. The adherents of the filtration theory, on the other hand, must also admit that secretion does take place in the kidney. When a substance is excreted in the urine in an amount many times exceeding that which can have been carried to the kidney by the blood flow during the same period, the assumption of secretion seems unavoidable.

**Definition of Terms** — Before proceeding it is best to define what we mean when we use the terms filtration, reabsorption and secretion in connection with processes in the organism generally.

As *filtration* we term a transport of fluid across a membrane through the action of hydrostatic pressure alone. If the fluid is separated from colloids by the filtration, we speak of *ultrafiltration*.

*Reabsorption* is usually defined as a process by which a substance, water or solid, is transported back into the blood again after having in some way left it. As this transport back may be effected in different ways, we may speak of active and passive reabsorption.

*Active reabsorption* occurs if the cells through which the transport takes place use energy to help the passage. The transport may then take place against the concentration gradient or may proceed faster than ordinary diffusion would allow.

*Passive reabsorption* takes place when a substance is brought back into the blood without the use of energy, by means of pressure and concentration differences existing between the fluid and the blood. Water may in this way be sucked into the blood if the colloid osmotic pressure of the latter is high enough to overcome the blood pressure.

If solid substances permeate through cells into the blood because their concentration is higher outside this is a simple process of diffusion

By nature

the outside through gland cells. The main point in this case is also whether the transport takes place at the expense of energy furnished by the vital activity of the cells. According to this definition secretion occurs (1) if a substance is transported from blood to the outside against a pressure or concentration gradient (2) if the substance transported is synthesized by the cells from constituents of the blood and (3) if a substance is stored in concentrated form in the cells and later excreted.

What has been proved? Which of these processes have been shown to exist in the kidney? Direct study of fluid within the excreting units of the kidney, glomerular capsules and tubules—are extremely difficult and until now have been made only in lower animals. Practically all that we know we owe to the work of Richards and his school. Through their work it has been made highly probable that the fluid excreted in the glomerular capsule is an ultrafiltrate of the blood. It is protein free its total molecular concentration is the same as that of blood the total amount of electrolytes is the same. It contains urea sugar chlorine potassium and injected dyes. Experiments by White show that the formation of the fluid is highly dependent on the equilibrium between colloid osmotic pressure plus capsule pressure on one hand and glomerular capillary pressure on the other hand. When these forces are in equilibrium fluid excretion practically stops and the experiments of this author to the writer's mind proves that ultrafiltration is the normal function of the glomeruli.

Wearn and Richards showed that even when the urine of the frogs contained no sugar or chloride these substances were present in the glomerular fluid. Reabsorption of these substances has thus been proved and also the reabsorption of water. Secretion too has been demonstrated. The synthesis of hippuric acid by the kidney is secretion and the far more important formation of ammonia must also be called secretion. But secretion in the sense of transport of preformed substances from the blood through the tubule cells into the urine with the use of cell energy has not been proved. Nor has a storing of substances with subsequent excretion

ption and secretion between the or their explanation hold that vital

activity is necessary and that energy is used. But while the

secretion theory holds that practically all the energy is used in transporting substances from the blood through the tubule cells out into the urine—that is for secretion—the other theory holds that the main use of energy is for transport in the opposite direction—that is for reabsorption. And while the secretion theory assumes that the amount of fluid excreted in the glomerular capsules is of about the same quantity as that of the urine during the same period the filtration theory assumes that far larger quantities are filtered so large in fact, that all the solids of the urine are present in the filtrate and most of them in far greater quantities than in the ultimately formed urine.

### MAGNITUDE OF THE FILTRATION

How large is the necessary quantity of filtrate? The quantity is certainly larger than usually assumed. In a number of experiments the author<sup>17</sup> tried to raise the creatinine content of the blood to such a level that it could be estimated fairly accurately. At the same time the creatinine excretion was followed with the result that creatinine was found to be excreted in amounts so large it was necessary to assume a filtration of 120 to 180 cc per minute or even more. The result has later been confirmed (Holten and Rehberg, Tolling, Poulsson). Creatinine is at the same time concentrated more than any other substance—a concentration ratio of 400 has been encountered.

But is it possible to filter 180 cc per minute through the glomeruli that is more than 250 liters in a day or about 100 times the total amount of blood plasma? The filtration or rather ultrafiltration through a membrane depends on different factors—the surface area and character of the membrane and the filtration pressure. How large is the surface of the glomeruli? To get an answer to this question we must know the surface of a single glomerulus and the total number of glomeruli in the human kidney. Both questions have been answered by the work of Vimtrup.

Vimtrup has shown that the glomeruli are even better adapted for filtration than is usually assumed. Each glomerulus consists of a number of capillary loops about 50 in all every capillary loop being covered with epithelium. The pictures usually given of the

for one glomerulus

Vimtrup has also given more reliable figures for the number of

glomeruli than the older data. His method has been controlled by three total counts of glomeruli in a kidney of rat, cat and man. The result is that the number of glomeruli in the human kidney may be put at 1,000,000. The total surface available for filtration would then be 1.5 sq m. Over this surface the blood is separated from the capsule by a membrane the thickness of which does not perhaps exceed  $1\ \mu$ .

Now the experiments of Landis have shown that the filtration through mesenterial capillaries in the frog can rise to 9 l cc per 100 sq cm for a pressure of 1 atmosphere before the capillaries become permeable to protein. Assuming the blood-pressure in the frog is 100 mm Hg, we should get 100 cc per 100 sq cm. As the permeability of the frog capillaries is much greater than that of the kidney capillaries, one must admit

that the formation of a filtrate in amounts of even 150 cc per min is possible.

We must, therefore, if we want to keep up the filtration-reabsorption theory, postulate that the first step in the excretion of the urine is the formation of 150 cc of ultrafiltrate each minute. From this filtrate most of the water is reabsorbed along with different substances. According to the formulation of the theory given by

tained. Experiments by Mayrs showed that part of the filtered urea was reabsorbed and was reabsorbed in varying concentrations. Experiments by the author confirmed this and showed that for chlorine, also, the concentration must vary within wide limits in the reabsorbed fluid. Recent experiments by Ni and the author have shown that sugar behaves in the same way. The reabsorbed fluid is not of constant composition, but varies according to the composition of the filtrate.

### THRESHOLD SUBSTANCES

The substances present in the reabsorbed fluid Cushny called "threshold bodies". The use of this term should indicate that when their concentration in the blood is below a certain threshold value they are not present in the urine. Following the experiments of Mayrs, which showed that urea is reabsorbed, he, and later Cushny, concluded that urea is a threshold substance. Now the experiments of the author showed that creatinine is concentrated more than all other substances, except perhaps a few which become concentrated to the same degree. This means that all other substances must become reabsorbed to some extent, i. e., that they are threshold substances. But if this is so, the original simple

theory of Cushny has lost most of its attractiveness and necessarily becomes very complicated. The mechanism of the reabsorption which Cushny conceived of corresponding to our term active reabsorption becomes very difficult to understand when it includes nearly all substances. The author therefore, tried to modify the theory so as to fit these new facts, attempting to retain the simplicity of Cushny's original theory. This led to the distinction between active and passive reabsorption which latter term here means backdiffusion. The reasons for this distinction may perhaps be made clear in the following way. Suppose we send a fluid con-

be a substance for which the walls are extremely permeable this substance will not be concentrated at all. As soon as any concentration difference between the fluid within the tube and that outside arises diffusion will take place and eliminate the difference. The substance will leave the end of the tube in the same concentration as it entered but the total amount will be much reduced—to the same extent as the water has been reduced.

TABLE 4

(Showing the concentrations of A alcohol (a highly diffusible substance) B urea (a moderately diffusible substance) C creatinine (a non diffusible substance) and D a threshold substance (one actively reabsorbed) after passing along a semipermeable tube through the wall of which water is being absorbed.)

		A Alcohol)		B (Urea)		C (Creatinine)		D (Threshold subst.)	
		Mg	Mg cc	Mg	Mg	Mg	Mg	Mg	Mg cc
Filtered	100 cc	10.0	10	10	10	10	10	10.0	10
Reabsorbed	50 cc	5.0	10	9	18	10	20	4.0	8
Remaining	50 cc								
Reabsorbed	90 cc	1.0	10	8	80	10	100	0.5	5
Remaining	10 cc								
Reabsorbed	10 cc	0.1	10	5	500	10	1000	0.03	3
Remaining	1 cc								

Let C be a substance toward which the walls of the tube are impermeable. When water is absorbed this substance will become concentrated and will leave the end of the tube in a concentration which is an index of the degree to which water has been reabsorbed. Suppose, finally, that B is a substance toward which the walls are moderately permeable. B will then be concentrated, but part of it will diffuse back and when it leaves the end of the tube it will be concentrated perhaps only one-half as much as C which means that only one-half of the substance is retained in the fluid while the other one-half has diffused back. The more concentrated the fluid becomes in regard to C, that is, the more water is reabsorbed,

the more will B become concentrated but more of B will also diffuse back so that the proportion is diminished

If the active process taking place in the tubules of the kidney is reabsorption of water while the walls of the tubules vary in degree of permeability toward different substances we can explain the behavior of substances which like A are not concentrated at all. Such substances are alcohol and acetone. If the walls of the tubules are impermeable to one or more substances these will behave like C to be concentrated more than others and their final concentrations will be an index of the degree of concentration of the urine. Substances of this kind are found in creatinine and sulphates. In between these extremes we find compounds toward which the walls of the tubules are permeable to some degree and which are therefore somewhat concentrated though never as much as creatinine but the more concentrated creatinine is the more concentrated will these substances be. Urea is such a compound.

present

or be

necessary to assume an active reabsorption. Substances for which this is necessary we call threshold substances but their number is not great.

### THE MODIFIED THEORY

The modification of the filtration reabsorption theory made necessary by the facts already mentioned may be formulated thus. The

- 2 -

#### 5. Secretion of substances not preformed in the blood

### EXPERIMENTAL EVIDENCE

With this scheme as a working hypothesis a number of experiments have been performed partly by the author and co-workers partly by others. The results of these studies which have so far confirmed the theory shall be briefly discussed.

1. **Creatinine as Index of the Filtration Rate** The basis of all the experiments is the assumption that creatinine can be used as an index of the filtration rate. The calculation of the filtration

rate per minute is carried out by means of the following formula,  $F = CV$ , where  $C$  is the concentration ratio of creatinine—i.e.,  $\frac{\text{(percentage in urine)}}{\text{(percentage in blood)}}$ —and here  $V$  is the urine volume per minute

If creatinine is really filtered through the glomeruli and does not diffuse back through the tubules, it should be possible to demonstrate certain facts which must follow from this (a) If a substance is excreted through the glomeruli by an ultrafiltration process the excretion of the substance shall be dependent on the filtration pressure. As the filtration pressure depends on the colloid osmotic pressure of the blood which counteracts it, the excretion of creatinine should vary inversely with the colloid osmotic pressure of the blood. Such is the case. In experiments together with Ni, the author has shown that in changing posture, the colloid osmotic

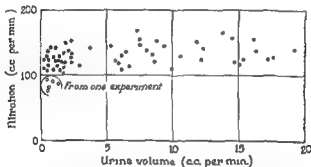


FIG. 8.—Independence of filtration and diuresis. From experiments on 1 normal subject (Holten and Rehberg *Acta med Scand*)

pressure of the blood varies much and the excretion of creatinine

altered at the same time, but the change in the colloid osmotic pressure is by far the dominating one (b) The excretion of a substance which does not diffuse back shall be independent of the degree of concentration of the urine. As volume of urine and degree of concentration of urine vary in opposite directions, it means that the excretion shall be independent of the volume of the urine. Creatinine practically is so (c) If other substances could be demonstrated to follow creatinine in concentration ratio, this would mean that they, too, do not diffuse back.

Poulsen, in a valuable contribution, demonstrated that the concentration of inorganic sulphate in the urine is proportional



to the creatinine concentration index. Poulsson has moreover contributed one of the strongest arguments brought forward in support of the theory namely, that in the completely phloridzinized dog sugar is concentrated very nearly to the same degree as creatinine. The only explanation possible under the secretion theory namely that a phloridzinized kidney begins to secrete sugar at nearly the same rate as that at which it secretes creatinine and sulphate is of course possible but certainly not probable.\*

**2 Threshold Bodies**—The excretion of two threshold bodies has so far been studied

(a) As mentioned above Poulsson demonstrated that sugar in the urine in the phloridzinized dog is not reabsorbed and experiments by Ni and the author threw light on the glucosuria caused by a high sugar level in the normal dog. Our experiments showed that sugar is reabsorbed even when the concentration of sugar is high above the normal and even reabsorbed in increased amounts but that the increase in reabsorption does not parallel the increase in filtration consequently more and more is excreted.

The reabsorption seems to be limited because the tubule cells are able to reabsorb sugar only against a certain concentration difference of sugar. When this limit is reached no more is reabsorbed and the remaining sugar is concentrated with the urine and excreted. Sugar is not reabsorbed in constant concentration but the percentage in the reabsorbed fluid increases with increasing blood sugar.

(b) *Chloride*—The reabsorption of chloride has been shown to be regulated in such a way that the kidney tries to keep up a chloride level of 370 mg per 100 cc<sup>18</sup>. At this level chloride is excreted

only traces of chloride are left in the urine. If the chloride in the blood is increased the percentage in the reabsorbed fluid is increased also but not so much and more and more chloride is excreted. Under these circumstances it is hard to distinguish between active and passive reabsorption and it is not possible to say how much can be explained by mere backdiffusion but probably all active reabsorption is stopped when the chloride level reaches 400 mg per cent.

\* Hober has demonstrated that creatinine is filtered through the glomeruli in the frog and that no creatinine is secreted by the tubules.

reasoning. If a substance is concentrated only 100 times when the urine has been concentrated 150 times it means that one-third of the filtered amount has diffused back, while two thirds are excreted. With a concentration index of 150 the urinary volume will be approximately 1 cc per minute. If the concentration is only one-

obtained in this way closely resembles that obtained experimentally for the excretion of urea. The experimental curve differs from the theoretical only in a somewhat larger backdiffusion with high urinary volume. The deviation is probably to be explained by an increase in the surface through which the diffusion takes place—an increase caused by the dilatation of the tubules when the diuresis is large.

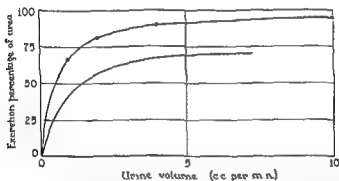


FIG. 9.—Curves showing the relation between urea excretion and urine volume. Upper curve drawn on the assumption that the back diffusion at a urinary volume of 4 cc is 10 per cent. Lower curve the values actually found. (Holtzen and Rehberg, *Acta med. Scand.*)

The most significant fact is that when the volume of urine is less than 2 cc the excretion of urea shall be highly dependent on the urinary volume and increase with it while it shall be almost independent at greater diuresis. This is exactly what Van Slyke and co-workers have demonstrated and the fact that the working hypothesis put forth here gives a natural explanation of this excretion curve shows its usefulness.

4 **Secretion**—Folling has used the creatinine method to confirm the finding of Nash and Benedict that ammonia excretion cannot be accounted for by filtration but that true secretion—that is synthesis—must take place in the kidney.

5 **Other Experiments**—Other experiments not having a special bearing on the theory might perhaps be mentioned.

Pouls<sup>15</sup> has beside the experiments on phloridzin glucosuria already mentioned made a study of the influence of pituitrin on the function of the kidney. He concluded that glomerular filtration rate is not markedly changed so the decrease in diuresis must be brought about by an increase in reabsorption. Moreover he demonstrated that urea under the influence of pituitrin diffuses back to a larger extent than usual a fact which he explains by assuming that the increased water reabsorption takes place in the upper part of the tubules so that the concentrated urea has to pass through a longer part of the tubules.

Experiments in the laboratory of Orbelli in Leningrad show the blood flow through the kidney of dogs is always large enough to allow the formation of the amount of filtrate necessary to explain the excretion of creatinine (Personal communication).

As a summary of this part we may say that the physiological experiments made heretofore are in such good agreement with the theory that it seemed justifiable to test it in the clinic partly in elaborating functional tests partly in explaining the pathological changes of function met with. Since the understanding of the function of the diseased organ is impossible so long as we do not attempt to look at it as modified normal function and since every physiological theory of the function of an organ must be able to offer some explanation of its dysfunction as well we might hope through a clinical study to gain results of value to the theory itself.

### THE PATHOLOGICAL FUNCTION OF THE KIDNEY \*

When we want to explain the pathological function of the kidney by means of the theory of the kidney we have to consider the following processes in the kidney: (a) Filtration + reabsorption + secretion + excretion. (b) Filtration + reabsorption + secretion + excretion. (c) Filtration + reabsorption + secretion + excretion. (d) Filtration + reabsorption + secretion + excretion. (e) Filtration + reabsorption + secretion + excretion. (f) Filtration + reabsorption + secretion + excretion. (g) Filtration + reabsorption + secretion + excretion. (h) Filtration + reabsorption + secretion + excretion. (i) Filtration + reabsorption + secretion + excretion. (j) Filtration + reabsorption + secretion + excretion. (k) Filtration + reabsorption + secretion + excretion. (l) Filtration + reabsorption + secretion + excretion. (m) Filtration + reabsorption + secretion + excretion. (n) Filtration + reabsorption + secretion + excretion. (o) Filtration + reabsorption + secretion + excretion. (p) Filtration + reabsorption + secretion + excretion. (q) Filtration + reabsorption + secretion + excretion. (r) Filtration + reabsorption + secretion + excretion. (s) Filtration + reabsorption + secretion + excretion. (t) Filtration + reabsorption + secretion + excretion. (u) Filtration + reabsorption + secretion + excretion. (v) Filtration + reabsorption + secretion + excretion. (w) Filtration + reabsorption + secretion + excretion. (x) Filtration + reabsorption + secretion + excretion. (y) Filtration + reabsorption + secretion + excretion. (z) Filtration + reabsorption + secretion + excretion.

by coalescence of the individual capillary loops (b) and (c) be reduced if the character of the membrane is changed (d) if it is thickened (e) If the filtration pressure is reduced either because the blood pressure itself is low or because the colloid osmotic pressure of the blood is too high the filtration will be decreased (f) If the total

ing to the extent to which they diffuse back. The excretion of substances not diffusing back, like creatinine and sulphate, will be reduced in proportion as the filtrate is reduced. Substances which diffuse back are reduced in amount in the filtrate, but their excretion may easily be normal if a more dilute urine is excreted. In this way decreased water reabsorption can have a compensatory action on the excretion of the diffusible substances, while the non-diffusible, like creatinine, are not influenced. Their concentration in the blood is not affected by filtration or reabsorption.

The filtration pressure may be reduced either for the reasons mentioned or because the intracapsular pressure is raised. The intracapsular pressure depends on the force necessary to drive the filtrate and later the urine through the tubules. How large the necessary pressure is we do not know—we do not even know for sure if the tubules have cilia which take part in the transport of the fluid\*. But if the reabsorption of water is decreased the amount of fluid which has to be driven out is larger and the intracapsular pressure will rise so that filtration is decreased. This means that pathological changes in the tubules which affect their reabsorption ability will influence the filtration through the glomeruli. Normal reabsorption is a condition for normal filtration.

**Testing of Glomerular Function**—When we want to test the function of the glomeruli we can, according to what has been said, do so by determining the amount of blood cleared of creatinine per minute. Our procedure has been the following:

blood sample drawn

The volume of this last sample of urine is measured and creatinine

$$\text{Concentration index} = \frac{1.200}{5.7} = 220$$

$$\text{Filtration rate} = \frac{220 \cdot 401}{60} = 147 \text{ cc per minute}$$

\* An observation by C. E. Lewis mentioned in Baetjer's paper on this old American physiologist is a strong argument in favor of the existence of cilia.

When we determine the filtration rate under these fairly standardized conditions we have found in normal persons values between 113 and 186 cc per minute. Values below 100 cc we regard as below normal. This test gives us information not about the state of the glomeruli but only about their function. From this alone we cannot say why filtration is decreased.\*

**The Functions of the Tubules and Tests for Them**—(a) The function of the tubules is of a very complex nature and consequently can be altered in different ways. The ability to reabsorb water may be decreased thus augmenting the urinary volume. A decreased ability for reabsorption cannot however be demonstrated except under conditions producing maximum concentration of the urine. This is done by the Volhard test by which the concentrating power of the tubules is certainly best estimated. The simplest procedure is to determine the maximum specific gravity obtained under the conditions of the test.

(b) The reabsorption of the various threshold substances can suffer—renal glucosuria is no doubt caused by insufficient reabsorption of sugar and we may find cases in which the reabsorption of chloride is altered so that chloride in spite of a much too low

normal. In these cases the regulation of the chloride reabsorption has failed.

(c) As it is an important part of the role of the tubules to keep the concentrated substances from diffusing back we can expect that an increased backdiffusion of urea would mean that urea with the urine is less

than should be expected at the concentration ratio of the urine. The percentage which is excreted—the excretion percentage as we have called it—is not however very constant even under normal conditions and changes in the excretion percentage must therefore be large before we can say definitely that the tubules are abnormally permeable.

One could expect perhaps that permeability might be increased for creatinine too, creatinine excretion then being no longer an index of filtration. This cannot be absolutely rejected but while we have met nothing which points toward such a possibility we have experiences which certainly point against it.

In urological cases where the ureter is obstructed we may find sometimes that the power of the diseased kidney to concentrate

\* In a series of normal children Holten (193) has found the filtration to be on an average of 83 cc per min per sq m body surface with a minimum of 60 cc per min per sq m.

urea is practically abolished while creatinine is still concentrated almost normally. The following case may serve as an example.

February 7 Ureter catheterization. On left side normal findings. Urine shows a concentration index of 200 while urea is concentrated 93 times. On right side the entrance of the catheter is stopped when 5 cm in the ureter. Only very little urine obtained. Urine shows a concentration index of 177 while urea is concentrated only 27 times.

February 10 The stone is discharged.

February 11 Urine from left side shows a concentration index of 101, with urea concentrated 33 times. Right side urine has a concentration index of 120 while urea is concentrated 34 times.

When a case like this shows a practically normal degree of concentration of creatinine (177 against 200 on the normal side) while urea is decreased from 93 to 27 times we take this as indicating that the urea has diffused back through the walls of the dilated tubules while creatinine has done so only to a small extent. The finding is also interesting from a theoretical standpoint as an explanation of the secretion theory demands the assumption that increased pelvic pressure interferes with the function of the cells responsible for secretion of urea but not with those responsible for secretion of creatinine.

The determination of the excretion of those substances which are secreted by the tubules must be separately made. The substance of the greatest interest is ammonia. We have records of cases where the secretion of ammonia was ten times larger on one side than on the other.

The conclusion from these considerations is that it is impossible to find a single test which will answer the question of how the kidney functions in every respect.

### SCHEME FOR TESTING THE FUNCTION OF A DISEASED KIDNEY

We suggest the testing of a diseased kidney in the following steps

- 1 Testing of glomerular function by determination of filtration-rate
- 2 Testing of tubular function
  - (a) Concentrating power determined by the Volhard concentration test
  - (b) Tightness of the tubules determined by comparison of urea excretion with creatinine excretion
  - (c) Reabsorption of threshold bodies especially chloride by comparison of chloride excretion with chloride level of the blood plasma
  - (d) Secretion of ammonia
  - (e) Regulation of pH. This is an important function but how it is carried out is not quite clear—possibly both the reabsorbing

and secreting mechanism is concerned. A number of cases have been studied but the theoretical significance of their disturbances is not yet elucidated.

### RESULTS OF CLINICAL STUDIES

By means of the tests outlined we have now studied a number of cases of which only a few shall be considered here. In our classification of the disease we have followed Volhard and Fahr, with the exceptions that we have separated essential hypertension (cases without albuminuria) from nephrosclerosis and have separated amyloidosis from the other nephroses—this latter because the albuminuria is of another type and edema is often absent.

**Acute Nephritis**—We have studied 6 cases from which we concluded that tubular function may sometimes be affected.

*Example Case 5*—Clinical histo

Later vomiting Headache no ex  
October 31 entered the hospital  
January 3 Blood pressure Octot  
Volhard Strauss test December 16  
1 010 February 17 specific gravity

TABLE 5

	Blood urea mg %	Filtration cc/min	Excret on percentage of urea
Nov 4	100	30	100
13	61	35	58 0
Dec 6	67	57	38 0
Jan 11	35	100	53 0
Feb 24	32	109	31 7

1 1 1 1 1 1 1

that even in these cases the tubular function may be involved—perhaps because the blood flow suffers through the anemia of the glomeruli. Practically the whole supply of blood to the tubules passes through the glomeruli and any obstruction to the glomerular blood flow must involve disturbances in the blood supply of the tubules as well.\*

**Chronic Glomerular Nephritis**—We had 17 patients in this group 2 of whom were in the second stage (maximum specific gravity at least 1 020). In the third (terminal) stage rates varying from no

The clinical picture of the patients and the degree of reduction in filtration-rate bore a close correlation

\* In a recent work Hou Jensen shows that at least about 97 per cent of all arterioles supplying the medulla of the kidney arise from vasa efferentia.

**Nephroses**—We have classified as nephroses cases with edema but without increased blood pressure and without hematuria. In this group we had patients showing normal or slightly reduced filtration values. In 1 of them the reduction occurred during a short period when a large number of casts were being excreted. Casts may block the tubules and in this way hinder the filtration. One patient whom we regarded as having a nephrotic contracted kidney had a filtration rate of only 5 cc.

Nephroses are good illustrations of the fact that a pathological change in an organ demonstrable histologically need not involve any functional change. The most significant feature of the histological picture of nephrosis is the degeneration of the tubules though no change can be demonstrated in their function. The glomeruli on the other hand are but slightly modified whereas the only functional change is the albuminuria which is undoubtedly of glomerular origin.

**Amyloidosis**—Four patients were observed with filtration rates from normal to 1.8 cc per minute or only one-eightieth of the normal value. One case was followed closely.

Albuminuria started July 1926. In May 1927 the filtration and blood urea were respectively 78 cc and 33 mg per cent. October 1927 42.5 cc and 60 mg per cent. January 1928 3.9 cc and 206 mg per cent. The patient died in uremia.

One other patient in this group also developed renal insufficiency. In both nephrosis and amyloidosis renal insufficiency is seldom marked. The comparative rarity of urinary symptoms in amyloidosis is because the patient usually dies from the underlying

heart symptoms. In 1 case we observed a distinct influence of the state of the heart action on the filtration. During an attack of arrhythmia the filtration was decreased to 6.8 cc whereas under the influence of digitalis the arrhythmia decreased while the filtration rose to 20.8 cc per minute.

**Essential Hypertension**—In these cases (5 in all) which we distinguish from nephrosclerosis by absence of albuminuria we found normal values in 4 instances (from 117 to 176 cc) but in



and 121 cc respectively and the maximum concentration power to be 1 015 and 1 016. The other case showed the same concentration power with a filtration rate of 108. Both cases point to an isolated tubular dysfunction.

**Discussion of Symptoms**—Following this brief review of our cases we wish to discuss a few of our findings of special interest together with some of the main symptoms of Bright's disease as elucidated by our material.

**Polyuria**—We picture the mechanism bringing on polyuria as follows. When the filtration rate is considerably decreased nitrogen retention in the blood begins. The result is that the glomerular filtrate contains a much higher concentration of nitrogenous substances than usual so that even with normal tubules the concentration limiting the reabsorption of water is reached at an earlier stage. Consequently a larger amount of fluid is left which cannot be reabsorbed, a condition even more pronounced if the tubules are injured also. The net result is that the concentration index of the urine is small and the excretion percentage of the backdiffusing substances is higher than it would be without the polyuria. The polyuria however can hardly be considered a compensatory mechanism of the kidney. We may with Volhard call it an obligatory polyuria.

**Hypothenuria and Isostenuria** would be explained in the same way as decreased ability to reabsorb water.

Attention is called to the fact that the isostenuria may be fully developed long before the filtration is reduced to the fatal limit. When the Volhard test shows variations in specific gravity between 1 009 and 1 010 it fails to give any further indications about the progress of the disease. Under these circumstances the filtration rate test will still be able to unveil an eventual downward course.

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**Uremia (Nitrogen Retention)**—In view of the fact that the degree of uremic symptoms and the nitrogen retention (urea retention) in the blood correspond closely it may perhaps be inferred that the cause of uremic symptoms is to be found in some nitrogenous substance.

The degree of urea retention depends on the equilibrium between urea production and urea excretion. The urea excretion is in most cases determined by the filtration rate of the kidney though in many cases the excretion percentage may be reduced so that it also contributes to the lowering of the excretion. We therefore, find a very marked correlation between filtration rate and urea content of the blood. As a rule we can say that as long as we have a filtration that is over 120 cc per minute we always find a blood

urea which is less than 40 mg per cent, with a filtration between 100 and 120 it may rise to 50 per cent. Serious urea retention does not occur until the filtration is decreased to about 60 cc per minute. It is very important to note that many cases with even a very low filtration rate show a normal blood urea partly because of the compensatory action of the polyuria partly because of low protein metabolism. Blood urea alone is not a good indicator of the state of the patient.

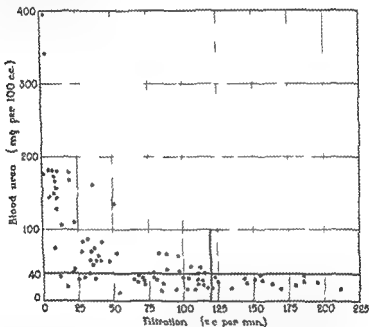


FIG. 10—Plots between blood urea and filtration rate in persons with and without kidney disease. Observe the number of cases in which the blood urea is normal while the filtration rate is low. (Holten and Rehberg *Acta med Scand*.)

The determination of the filtration rate has a high prognostic value in these cases as it allows one to determine the seriousness of an elevated blood urea. A blood urea of 150 mg is much more serious with a filtration of 10 cc per minute than it is if the filtration is 60 cc per minute. In the latter case it is almost certain that diet combined with a polyuria provoked by the ingestion of large amounts of water will be able to reduce the blood urea to a normal value. As a rule, we can say that when the filtration is 40 cc per minute

In the beginning - - - - -  
 No edema }  
 100 cc Volhard  
 gravity, 1.005  
 Blood urea, 80 mg per cent      Diuresis, 1500 to 2000 cc

He was put on a diet of fat and carbohydrate with only 40 gm of protein and receives, moreover, about 200 cc. extra fluid daily, thus maintaining a diuresis of about 3500 cc. In this way he has been kept in working condition as a teacher for two years. The filtration tests have shown the following:

TABLE 6

Date	Filtration cc per min	Blood urea mg per cent
Oct 20 1928	41	73
Dec 5 1928	37	75
Feb 1 1929	36	71
Mar 13 1929	26	85
May 12 1929	37	80

The exacerbation in the state of the patient shown by the filtration and by the blood urea on March 13 was due doubtless to the fact that the patient had a strenuous character water-drinking filtration-rate in any of the filtration test with those from the Volhard concentration test we believe we obtain a better picture of the state of the kidneys than was previously possible. We are able to follow closely variations in the degree of the disease and are often enabled to draw conclusions both with regard to prognosis and with regard to therapeutics.

The hypothesis has come for a hypothesis in

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## CHAPTER V

### THE EXCRETION OF THE NON-METABOLIZED SUGARS IN THE DOGFISH, THE DOG AND MAN

By HOMER W. SMITH, Sc D

**Introduction**—A substance suitable for measuring glomerular filtration must obviously be completely filtrable from the plasma, it must be physiologically inert, at least so far as renal function is concerned and readily amenable to quantitative determination in both plasma and urine. In addition, it must be neither secreted nor reabsorbed by the renal tubules, ureters and bladder. Of these several criteria the most difficult to establish as universally valid are those concerning secretion and reabsorption.

In seeking a substance fulfilling these requirements the author was led to the investigation of the non metabolized sugars by Marshall and Grafflin's<sup>18, 19, 20</sup> observation that glucose is excreted in the urine by glomerular but not by aglomerular fishes. On broad principles the author related this circumstance to the fact that, being a food and not a waste product, glucose has been conserved by the vertebrates throughout their evolution, and at no time continuously rejected from the body. The excretory organs have never been called upon, therefore, to secrete this substance, and were possibly incapable of doing so. The appearance of glucose in the urine of glomerular animals during hyperglycemia or phlorizin poisoning was in this view referable to the incomplete tubular reabsorption of this substance from the glomerular filtrate. (The circumstance of filtration and subsequent reabsorption of glucose or other substances is apparently one that owes its origin to the course of evolution of the glomerular vertebrate kidney—Smith<sup>25, 26</sup>) Because it is normally reabsorbed by the tubules, glucose itself is not suitable for the evaluation of glomerular filtration, and although this reabsorption can be arrested by phlorizin there is no reason to believe that other physiological activities of the  
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the  
tubules other sugars might not be secreted by them, and that, among the metabolically inert sugars one or more might be found that were not reabsorbed as was this physiologically important

fuel-stuff. Consequently, investigations were undertaken in this laboratory on the excretion of non-metabolized sugars, xylose<sup>4-7 22</sup> and sucrose<sup>7 17 21 22</sup>

Since conclusions drawn from a single species must be viewed with some uncertainty, these investigations have been extended to include the dogfish, the dog and man as fair extremes of the chordate phylum

THE EXCRETION OF NON-METABOLIZED SUGARS BY THE DOGFISH

The dogfish, *Squalus acanthias*, was chosen for the practical

the Elasmobranch fishes for the purpose of maintaining the osmotic pressure of the blood (Smith<sup>23 24</sup>) That the failure of the elasmobranch kidney to excrete this freely diffusible substance is the result of active conservation (tubular reabsorption) is indicated by the fact that during diuresis and under other circumstances the urea concentration in the urine rises and approaches that of the blood

The earlier experiments of Clark and Smith<sup>2</sup> showed that xylose was copiously excreted by the kidney of this animal The administration of phlorizin immediately induced an excretion of glucose (as it does in all vertebrates so far examined) to such an extent that the glucose clearance approximated the xylose clearance, although the xylose clearance was not increased More recent experiments by Shannon<sup>25</sup> furnish additional evidence on this point In Table 7 there are given simultaneous clearances (in the phlorizinized dogfish) of glucose and xylose on the one hand and of glucose and sucrose on the other, as well as the simultaneous clearances of xylose and sucrose in the normal animal Xylose and sucrose (the latter after parenteral administration, of course) are handled as

and also by agnathous fish (*Coryphæus latidorsalis* and *Lophius piscatorius*), while not even traces of sucrose diffuse across the tubules of *Lophius* In two unpublished experiments of Clarke's, the plasma, after the intravenous injection of sucrose, contained 540 and 1060 mg per cent, respectively, of this substance Urine collected over the following four-hour period had less than 1 mg per cent of sucrose

in it Not only does this show that sucrose is not secreted by the aglomerular tubule of *Lophius*, but that diffusion of this substance across the tubule from the blood to the urine is so small as to be entirely negligible. As between two fish, the inability of the aglomerular kidney to secrete xylose and sucrose would argue strongly for a similar inability in the glomerular kidney, but to support this inference there is the observation of Marshall and Grafflin,<sup>20</sup> that glucose disappears entirely from the urine of the glomerular sculpin when the glomeruli are closed by large doses of phlorizin.

TABLE 7—COMPARISON OF THE GLUCOSE, XYLOSE AND SUCROSE CLEARANCES IN PHLORIZINIZED DOGFISH AND XYLOSE AND SUCROSE CLEARANCES IN NORMAL DOGFISH \*

Experiment No.	Total concurrent time hrs.	Urine volume cc/kg/day	Glucose		Xylose		Clearance cc/kg/day		Ratio
			Plasma mg per 100 cc	Urine mg per 100 cc	Plasma mg per 100 cc	Urine mg per 100 cc	Glucose	Xylose	
53	33	44.0	83	129	210	320	69.6	66.0	1.03
	45	32.0	80	136	174	289	54.4	53.1	1.03
	57	28.0	79	136	180	258	49.8	48.8	1.03
55	33	46.2	116	201	140	244	80.0	80.4	0.99
	45	37.5	110	198	123	234	67.6	71.2	0.95
	57	26.0	103	252	109	272	64.0	65.3	0.98
3					Sucrose			Sucrose	
	21	38.0	231	531	193	454	87.5	89.3	1.02
	23	34.7	218	545	170	421	86.8	86.1	1.01
	26	26.6	214	652	167	503	80.8	83.3	1.03
	26	18.7	212	727	153	497	64.1	60.8	0.95
4	32	24.7	211	670	145	436	78.3	74.4	0.95
	21	46.9	248	433	306	497	82.1	76.0	0.93
	23	35.7	194	447	267	533	82.1	77.8	0.95
	26	28.8	181	448	254	637	64.0	64.4	1.01
	28	27.2	172	432	243	638	68.3	71.3	1.04
1	32	36.0	162	345	232	475	76.6	73.8	0.96
			Xylose				Xylose		
	23	8.9	148	612	356	1632	36.8	37.6	1.02
	26	12.2	132	611	363	1431	47.3	48.1	1.02
			Xylose						
II	23	7.2	162	822	370	1767	36.5	34.4	0.94
	26	7.6	148	718	364	1705	36.9	35.7	0.97

\* Summaries of these experiments are given by Shannon.<sup>22</sup>

The above evidence is wholly consonant with the supposition that glucose, xylose and sucrose are excreted exclusively by glomerular filtration, xylose and sucrose passing down the lumen of the tubules, where the glucose is actively reabsorbed, except in the phlorizinized animal where its reabsorption is partially or completely blocked.





as the plasma level is raised to higher values the creatinine clearance falls and approaches the xylose clearance asymptotically (see Marshall and Grafflin<sup>20</sup> for the initial observations on this point). The full import of Shannon's experiments is conveyed effectively by Fig 11, compounded of data from several dogfish.

The rate of excretion of a non reabsorbed substance excreted exclusively by filtration all other factors remaining constant must increase in direct proportion to the plasma level that is the clearance will be independent of the plasma level. No explanation is evident for the observed curvilinear relationship in the dogfish between creatinine clearance and plasma level other than secretion and Shannon's analysis of his results suggests that the fraction of creatinine cleared from the plasma over and above filtration is such that a constant amount of energy would be necessary to accomplish the secretion of this substance. Though the problem cannot be approached thermodynamically at the present time the evidence is such as to be readily reconciled with the apparent secretion of a considerable quantity of creatinine by the tubules in addition to that which is filtered and to be unreconcilable with an exclusive process of filtration.

The fact that phlorizin depresses the creatinine clearance from a level six times as great as the xylose clearance to a level less than twice as great without raising the absolute value of the xylose clearance itself indicates that the excretion of creatinine is effected by some unstable and easily injured mechanism. It is not evident how phlorizin could impair the glomerular excretion of creatinine nor is there anything to support the belief that this drug would stimulate a supposititious reabsorption of creatinine while blocking the accepted reabsorption of glucose and leave a supposititious absorption of xylose and sucrose unchanged.

All the evidence from the dogfish then points to the belief that creatinine is excreted in part by tubular secretion and in part by glomerular filtration while xylose and sucrose are excreted exclusively by the latter route without the reabsorptive process that is normally present for glucose.

### THE EXCRETION OF NON-METABOLIZED SUGARS BY THE DOG

The dog appears to resemble man more closely in respect to renal function than any other animal on which extensive information is available at the present time. For this reason the dog has been chosen as the principal experimental animal in the study of mammals. The data given in Table 8 are representative of the results obtained in the laboratory of the Department of Physiology of the New York University and Bellevue Hospital Medical

# EXCRETION OF NON-METABOLIZED SUGARS BY DOG 97

TABLE 8—COMPARISON OF XYLOSE AND SUCROSE CLEARANCES IN NORMAL DOG

Experiment No.	Total concurrent time min.	Urine volume cc/min.	Xylose		Sucrose		Clearance cc/kg in 1 min.		Xylose	Sucrose
			Plasma mg per 100 cc	Urine mg per 100 cc	Plasma mg per 100 cc	Urine mg per 100 cc	Xylose	Sucrose		
85	32	1 04	(From Jolliffe 94 1 1652	109 2	Shannon and Smith <sup>11)</sup> 1840	33 7	34 4	1 02		
	60	1 09	106 4	2019	102 4	2116	34 3	41 7	1 09	
	90	1 03	116 4	2046	115 2	2708	34 2	38 2	1 12	
86	31	1 03	95 8	4025	101 5	4075	57 0	52 7	0 92	
	60	1 17	105 2	4130	109 8	4394	60 6	62 2	1 03	
	92	1 22	101 3	3520	109 1	4210	60 6	62 0	1 02	
120	22	1 63	(From Jolliffe Shannon and Smith <sup>11)</sup> 3410	111 0	2445	119 7	124 1	0 97		
	43	1 91	176 0	2946	106 0	112 9	111 0	1 02		
	60	4 47	176 0	255	101 0	1926	110 4	109 0	1 01	
140	20	2 05	212 0	3400	204 0	3270	35 8	35 0	1 02	
	60	2 20	219 0	1625	216 0	4040	49 6	39 7	1 00	
	70	2 10	178 0	3355	256 0	4450	41 0	43 3	0 99	
22	10	2 55	144 0	835	173 0	765	26 7	26 6	1 00	
	21	1 42	139 0	960	145 0	1010	22 9	23 0	1 00	
	53	1 25	124 0	1130	151 0	1115	20 1	19 8	0 99	
83	10	6 40	146 0	1090	122 0	775	75 0	77 0	1 03	
	21	4 76	171 0	1370	112 0	875	76 2	74 4	0 94	
	31	1 62	157 0	1725	103 0	1170	79 6	80 8	1 01	
214	11	4 69	112 0	(From Shannon unpublished) 1090	219 0	2115	63 8	63 6	1 00	
	26	5 62	117 0	112	259 0	2000	56 2	60 0	1 07	
	39	6 40	121 0	159	273 0	2000	67 2	69 4	1 03	
217	10	8 90	123 0	724	144 0	1070	43 0	41 8	0 97	
	21	6 00	124 0	711	192 0	1113	41 8	42 4	1 01	
	32	6 51	130 0	680	215 0	1115	41 7	41 3	0 99	
218	10	3 50	127 0	846	153 0	1000	32 1	30 1	0 94	
	21	1 25	124 0	919	172 0	1170	30 9	23 1	0 93	
	31	3 40	130 0	942	149 0	1365	32 7	31 4	0 96	
212*	10	6 00	116 0	1095	262 0	2440	65 8	75 6	1 15	
	21	7 31	122 0	848	271 0	110	62 0	75 6	1 22	
	31	5 40	126 0	1199	274 0	3040	64 2	76 0	1 18	

\* Delivered of pups two days after this experiment

College and show that in the normal dog the simultaneous clearances of xylose and sucrose are identical within the limits of experimental error in the determination of the sugars. In experiments with phlorizinized dogs the trisaccharide, raffinose, shows the same clearance as glucose (Jolliffe, Shannon and Smith<sup>11)</sup>, since

xylose, sucrose and glucose give identical clearances under these same conditions it appears that these sugars are all handled in the same manner by the kidney

The question of whether or not phlorizin completely blocks the active reabsorption of glucose is not open to direct investigation, but evidence bearing upon it can be obtained from the behavior of the various substances studied. The administration of phlorizin sometimes leads to a drop in the absolute xylose clearance, for unexplained reasons. It is a well-known fact that the urea clearance is characteristically inconstant, both in the dog<sup>11, 13, 14</sup> and in man, and we may tentatively ascribe this to variations in blood flow, glomerular pressure etc. It has been observed that the xylose clearance is equally variable in the normal dog,<sup>17</sup> and it is not unwarranted to conclude that phlorizin produces transient but significant changes in the clearance of xylose. However, it is significant however, that phlorizin does cause a rise in xylose clearance, and this fact in itself would indicate that there is no extensive reabsorption of xylose that is blocked by phlorizin. It might be that a drop in glomerular

for the measurement of glomerular filtration that can be placed definitely on independent grounds beyond the influence of this drug. But it is significant that the simultaneous xylose and urea clearance maintain a fairly constant ratio both in the dog<sup>12, 20, 21</sup> and in man<sup>2, 10</sup> and it is the exception rather than the rule for phlorizin to cause the xylose clearance to rise relative to the urea clearance. Since it is unlikely that phlorizin blocks the reabsorption of urea and xylose to precisely the same extent, and at the same time reduces the true glomerular clearance to the same degree (thus keeping the total clearance constant) it appears that there is no reabsorption of xylose that is blocked by this drug.\*

It may be noted that second and massive injections of phlorizin do not increase the excretion of glucose over the rate obtained by a minimum effective dose and on this *prima facie* evidence it is difficult to believe that the drug blocks the reabsorption of part of the filtered glucose and fails to block the reabsorption of the rest. But admitting the possibility it is then necessary, in order to

the xylose, sucrose and glucose clearances are identical within

\* Work completed in this laboratory since the preparation of this paper has led the author to question this point. The reader is referred to the note appended to the end

margin of a few per cent. In view of the way these several sugars are handled in the normal animal this reasoning appears to us to be futilely circumlocutionary.

these sugars by  
a matter can be  
to consider the

anatomy of the kidney. Practically all physiologists have agreed that the structure of the glomerulus is such as to promote easy diffusion and therefore easy filtration. The corollary is this anatomical interpretation is that the structure of the tubule is such as to restrict diffusion and therefore to permit the specific operation of reabsorption (or secretion). To overlook this fact is to disregard the one fundamental contribution that anatomy can make to this subject.

It is more to the point perhaps to recall that not even traces of sucrose diffuse from the blood through the tubules of the glomerular fish to appear in the urine. It is an improbable assumption then to suppose that these sugars diffuse in the reverse direction that is from the urine into the blood in either the fish or the dog. Diffusion in the proper meaning of the word must occur with equal facility in either direction or it ceases to be diffusion and becomes active reabsorption mediated either chemically or by a Maxwell demon.

But still more immediately the U/P ratio of urea in the dog may reach values of 300 (Rall, Brown and Pariente<sup>7</sup>) or higher and this substance is one of the most diffusible known. In view of the fact that such high concentration gradients of urea can be effected by the dog kidney it is *a priori* unlikely that the tubules are very permeable in the proper sense to substances like glucose, xylose and sucrose. But with the view of securing more certain evidence Jolliffe, Shannon and Smith<sup>11</sup> chose three sugars differing widely in molecular weight and therefore in diffusibility for their experiments in the dog. Finding no significant difference in the clearances of xylose (m.w. = 150), sucrose (m.w. = 342) and raffinose (m.w. = 504) and with only a 30 per cent discrepancy between the clearance of urea (m.w. = 60) on the one hand and the clearances of the three sugars on the other they were convinced that these

gated. In the diseased kidney or in the normal kidney at very low urine flows where there is a correspondingly high U/P ratio it may be that there is some small backdiffusion of sucrose or xylose. This problem can hardly be investigated with confidence until some substance of large molecular weight and still lower diffusibility, which checks xylose and sucrose at high urine flows is available.)

xyl

Jol

in the dog (1.3 to 1.5) than in the dogfish (4.2 to 7.2) due in part perhaps to intrinsically greater secretory capacity in the latter but it must also be noted that the fish tubules receive a copious supply of venous blood by way of the renal portal system that does not reach the glomeruli and that is therefore not available for filtration. The creatinine clearance in the normal dog is sufficiently above the xylose and sucrose clearance however to indicate that creatinine is removed from the blood by tubular secretion as well as by filtration.

A curvilinear relationship between the creatinine clearance and the plasma level of this substance has not been demonstrated in the dog (Shannon Jolliffe and Smith<sup>21</sup>) but to date the creatinine clearance has been studied at relatively narrow plasma-creatinine levels and such a relationship cannot be definitely excluded at this time.

TABLE 9—COMPARISON OF GLUCOSE, XYLOSE AND CREATININE CLEARANCES IN DOG BEFORE AND AFTER PHLORIZIN

Experiment No	Total excreted time	Urine volume cc/min	Xylose		Glucose		Creatinine		Clearances cc/sec./min			Ratios		
			Plasma mg per 100 cc	Urine mg per 100 cc	Plasma mg per 100 cc	Urine mg per 100 cc	Plasma mg per 100 cc	Urine mg per 100 cc	Xylose	Glucose	Creatinine	Glucose/Xylose	Creat/Xylose	
160					(From Shannon Jolliffe and Smith <sup>21</sup> )									
	0	3.50	180	272	77	0.0	24.4	412	59.4	0.0	87.0	0.0	1.00	
	49	7.62	19	2000	78	0.0	2.0	457	56.8	0.0	75.5	0.0	1.33	
	11	2.73	177	2886	76	0.0	19.5	390	61.8	0.0	70.8	0.0	1.23	
										A	67	0.0	1.32	
	106	2.63	145	After phlorizin (400 mg/kg)	1158	17.5	273	54.2			56.9		1.05	
	135	2.34	115	2150	89	1574	15.6	278	58.4	59.4	57.9	1.0	0.99	
	16	2.14	87	2069	76	1535	13.9	283	61.6	60.3	61.6	0.98	1.00	
										A	61.6	1.00	1.01	
71	10													
	21													
	31													
	42													
	81													
75	10	4.95	88	After phlorizin (400 mg/kg)	791	786	23.0	211	73.3	81.7	74.4	1.11	1.0	
	11	4.65	85	841	85	918	2.6	222	75.0	82.0	74.9	1.09	1.00	
	30	4.83	81	823	90	1029	21.9	225	80.8	91.0	81.3	1.12	1.01	
										A	81.3	1.11	1.01	

The supposedly secretory nature of the excess creatinine clearance in the dog is confirmed by the action of phlorizin. Data on the effect of phlorizin on the glucose and creatinine clearances are given

in Table 9. The administration of this drug temporarily reduces the creatinine clearance to the xylose or sucrose clearance, even while it brings the glucose clearance up to the same level (Shannon, Jolliffe and Smith<sup>21</sup> Pitts<sup>26</sup>).

Further evidence on the matter of glomerular filtration in the dog is furnished by the observations of Pitts<sup>26</sup> on the excretion of inorganic phosphates after intravenous injection. The phosphate

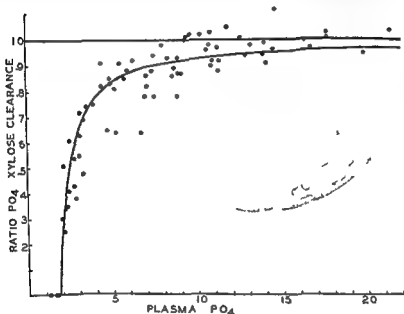


FIG. 12 — The ratios of the phosphate clearance to the xylose clearance are plotted

this time

clearance rises as the plasma level rises, and approaches the xylose or sucrose clearance without ever exceeding the latter (Fig. 12). Apparently some definite amount of phosphate (related perhaps, to the plasma and urine concentrations) is reabsorbed from the glomerular filtrate by the tubules, this moiety exerts less and less

clearance so that the latter no longer bears its natural relationship to the plasma level (White and Monaghan<sup>27</sup> Pitts<sup>28</sup>) but even in the presence of phosphate the drug continues to bring the glucose clearance up to and the creatinine clearances down to the level of the xylose clearance (Pitts<sup>28</sup>) It is apparently the excretion of phosphate that is affected and not the excretion of the other substances

White and Monaghan<sup>27</sup> have failed to observe the above identity with respect to  
to creatinine in  
these experimen

discrepancies between the results obtained in the St. Louis laboratory and the author. In only 2 dogs have highly discrepant ratios between the apparent xylose and sucrose clearances been obtained a result that may have been influenced by the presence of lactose in the blood and urine (for example see Experiment 212 Table 6) Otherwise the results confirm the original conclusions of Jolliffe Shannon and Smith<sup>11</sup> In no case has the creatinine clearance failed to approximate the clearance of the non metabolized sugars or glucose after adequate doses (100 mg per kg) of phlorizin Lack of space prohibits a discussion of the possible reasons for the conflicting results obtained by White and Monaghan and the investigators in this laboratory (See Pitts 4m *J Physiol* 542 109 1934)

#### THE EXCRETION OF NON METABOLIZED SUGARS BY MAN

Keith Power and Peterson<sup>6</sup> have examined the excretion of sulphate urea sucrose and creatinine in normal man and find average clearance values of 35 50 100 and 140 to 200 respectively More recently these same investigators have examined the simultaneous clearances of xylose and sucrose in normal man and find that the former averages 10.5 per cent lower than the sucrose clearance<sup>13</sup> These investigators remark Although the differences were not greater than might be expected from analytical errors it seems improbable that such errors would fall uniformly in one direction In spite of this it must be concluded that these sugars are excreted by the kidney in a similar manner

Similar comparisons of xylose and sucrose have recently been made at Bellevue Hospital by Dr. Herbert Chasis the results of which are published for the first time in Table 10 The author is indebted to Dr. Chasis for permission to include them here When due allowance is made for probable sources of error the relatively low plasma xylose superimposed on naturally occurring non  
of an ascending plasma  
asma sucrose curve with  
A 1 difference of these  
substances and the not inconsiderable difficulties attending the

analysis of mixtures of two foreign sugars in the presence of glucose—the results of these experiments may be accepted as evidence of the essential equivalence of the simultaneous xylose and sucrose clearance in normal man. The fact that in these experiments the sucrose/xylose ratio is greater than 1 is not evidence in the author's opinion that these sugars are handled differently, as White<sup>2</sup> and

TABLE 10—COMPARISON OF XYLOSE AND SUCROSE CLEARANCES IN NORMAL MEN  
UNPUBLISHED EXPERIMENTS OF DR HERBERT CHASIS\*

Subject	Dose mg/kg	Total excretion mg/min	Intravascular volume ml/min	Xylose		Sucrose		Clearance cc/min		Ratio
				Plasma mg per 100	Clearance ml per 100 cc	Plasma mg per 100	Clearance ml per 100 cc	Xylose	Sucrose	
C R 9	1.53	14	4.00	77.4	1127	76.3	6053	43.7	47.8	1.09
		34	4.00	71.1	1475	703	6849	54.0	59.0	1.09
		59	3.96	7.2	1.04	25.3	4306	47.6	43.0	1.03
		63	3.46	77.4	1731	190	4693	50.6	54.0	1.07
M B 9	1.37	21	4.00	37.9	595	4.4	7201	48.5	5.4	1.05
		16	3.97	30.0	670	376	6616	46	51.8	1.12
		8	3.08	34.5	617	334	6460	39.4	42.6	1.04
		71	2.64	3.6	711	90	674	49.0	47.7	1.11
H O 8	1.6	70	6.31	60.4	1004	731	4073	57.8	60.4	1.05
		40	6.70	60.1	1046	704	3903	60.2	66.7	1.10
		59	5.31	59.8	10.1	1.9	3147	55.6	57.0	1.03
								Aver		(1.04)

\* From the Department of Physiology, New York University and Bellevue Hospital Medical College and the Third Medical Division, Bellevue Hospital.

Chasis, Jolliffe and Smith<sup>3</sup> have shown that single intravenous doses of phlorizin of adequate size raise the glucose clearance in man to the level of the xylose and sucrose clearance. Data from their experiments are included in Tables 11 and 12. Once the reabsorption of glucose is completely blocked the simultaneous glucose, xylose and sucrose clearances remain identical within experimental error regardless of how much phlorizin is given (between the limits of 12 and 60 mg. per kg.). In view of this fact and in view of the further facts that the xylose clearance is not raised significantly in respect to the simultaneous urea clearance nor in respect to its own control level by the administration of phlorizin it appears that in man as in the dog and the dogfish xylose and sucrose are neither secreted nor reabsorbed.



# 104 EXCRETION OF THE NON-METABOLIZED SUGARS

TABLE 11 — COMPARISON OF XYLOSE GLUCOSE UREA AND CREATININE CLEARANCES IN MAN FOLLOWING INTRAVENOUS ADMINISTRATION OF PHLORIZIN<sup>1</sup>

Subject	Phlorizin mg per kilo	Surface area sq m	Total concurrent time min	Urine flow per min cc	Clearances cc/kg in/min				Creatinine Xylose	Urea Xylose	Glucose Xylose
					Xylose	Glucose	Creatinine	Urea			
M M ♀	6.07	1.52	31	3.20	18.4		43.2	14.5	2.35	0.79	
			63	3.20	34.3		78.5	26.5	2.29	0.77	
			90	Washout period							
			121	2.60	30.8	31.0	65.1	26.8	2.11	0.87	1.01
			150	3.60	37.6	34.6	86.4	32.5	2.30	0.86	0.93*
A H ♀	11.80	1.27	179	3.10	36.5	15.3	83.2	30.2	2.28	0.83	0.42*
			18	12.70	59.0		106.7	44.0	1.84	0.76	
			74	Washout period							
			94	3.20	49.1	50.3	86.2	38.8	1.76	0.79	1.02
			114	3.10	52.2	55.2	93.6	40.2	1.79	0.77	1.00
M S ♀	15.70	1.39	130	2.90	55.4	57.6	94.0	40.8	1.70	0.74	1.04
			25	1.60	53.5		96.3	41.7	1.80	0.78	
			72	Washout period							
			90	1.67	43.9	45.4	75.5	31.0	1.72	0.71	1.03
			104	1.63	42.3	44.2	73.0	30.7	1.73	0.74	1.04
C S ♀	20.40	1.47	130	1.75	45.6	45.3	81.2	34.3	1.67	0.71	0.99
			21	7.30	55.6		109.5	14.3	1.87	0.88	
			41	2.60	60.6		112.3	35.4	1.85	0.89	
			74	Washout period							
			94	2.37	52.4	54.0	105.5	30.6	2.01	0.88	1.03
N O ♀	65.20	1.60	115	2.25	55.4	56.0	108.5	33.1	1.96	0.80	1.01
			139	2.26	58.0	56.6	110.9	34.9	1.91	0.80	0.99
			20	9.70	42.0		76.3	33.1	1.77	0.77	
			44	6.02	41.4		82.5	34.3	1.99	0.83	
			91	Washout period							
			106	2.09	30.8	33.4	46.3	20.0	1.50	0.65	1.09
			126	2.10	32.9	34.3	49.9	20.7	1.52	0.63	1.04
			145	1.94	30.2	32.6	49.0	19.4	1.61	0.64	1.06

\* Incompletely phlorizinized

TABLE 12 — COMPARISON OF XYLOSE SUCROSE AND GLUCOSE CLEARANCES IN MAN FOLLOWING INTRAVENOUS ADMINISTRATION OF PHLORIZIN<sup>1</sup>

Subject	Phlorizin mg per kg	Surface area sq m	Total concurrent time min	Urine flow per min cc	Clearances cc/kg in/min			Glucose	
					Xylose	Glucose	Sucrose	Xylose	Sucrose
F M ♀	29.7	1.32	19	4.30	55.7	50.9	53.8	0.91	0.97
			39	3.95	55.4	55.4	53.6	1.00	0.97
			64	3.48	53.3	51.1	54.3	1.01	1.02
V T ♀	41.9	1.59	31	4.90	46.8	41.0	45.0	0.88	0.96
			51	3.50	37.8	34.7	35.6	0.92	0.94
			75	5.79	48.4	45.5	48.4	0.94	1.00
W M ♂	45.3	1.49	20	4.02	42.0	39.8	42.0	0.95	1.00
			43	3.97	47.0	45.9	46.1	0.98	0.98
			66	4.09	49.5	48.1	50.0	0.97	1.01
F M ♀	59.4	1.32	87	3.77	47.8	48.1	47.4	1.01	0.99
			29	4.30	55.1	56.0	58.6	1.02	1.06
			54	3.56	57.2	57.7	61.4	1.01	1.07
			82	2.86	46.2	44.8	48.5	0.97	1.05
			104	2.18	44.3	44.0	45.7	0.99	1.03

# EXCRETION OF NON-METABOLIZED SUGARS BY MAN 105

TABLE 13.—COMPARISON OF XYLITOL, UREA AND CREATININE CLEARANCES IN NORMAL MEN. SUMMARIES OF TIME DATA HAVE BEEN PUBLISHED BY JOLLIFFE AND CHARIS<sup>10</sup>

Subject	Age	Sex	Height cm	Xylitol		Urea		Creatinine		Clearances cc/kg/min		Ratio		
				mg per 100 cc	mg per 100 cc	mg per 100 cc	mg per 100 cc	mg per 100 cc	mg per 100 cc	Xylitol	Urea	Xylitol	Urea	
J. R.	27	M	173	57.6	3130.0	23.6	13.0	5.2	4.6	0.64	7.0	119.2	1.84	0.9
J. M.	104	M	1	8	4250.8	10.3	13.0	5.3	64.7	10.7	110.2	1.94	0.78	
F. M.	18	F	1	0	1073.0	33.8	183.0	9.7	54.0	47.2	10.5	73.5	1.56	0.8
H. J.	120	M	2	12	2110.0	17.7	616.0	7.0	446.0	6.5	41.8	113.3	1.34	0.87
C. H.	8	M	2	4	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
M. I.	76	M	11	4	431.0	76.5	1.4	7.5	154.0	54.3	41.9	111.0	2.4	0.77
K. T.	81	M	7	3	7.0	7.7	184.5	8.8	168.0	49.7	31.1	84.1	1.74	0.68
I. I.	210	M	7	6	41.0	23.6	1.4	1.0	311.0	43.1	24.8	72.1	1.6	0.88
A. R.	18	M	0	3	2.7	3.6	174.9	11.2	155.0	40.4	25.6	77.0	1.81	0.6
C. C.	177	M	10	0	43.4	21.7	225.0	8.0	243.2	57.0	34.8	99.2	1.78	0.0
J. H.	17	M	1	1	1.14	33.8	1091.7	11.8	43.6	11.7	83.0	1.71	0.0	
H. I.	18	M	4	8	314.0	1.3	78.7	1.9	31.6	42.4	7.3	87.7	1.80	0.62
J. H.	18	M	4	4	1746.0	74.7	1074.0	0.5	386.0	47.6	3.6	76.0	1.79	0.84
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
J. H.	18	M	1	4	1.3	1.3	1.3	1.3</						

Jolliffe and Chasis<sup>10</sup> have shown in 13 medical students that the creatinine clearance exceeds the xylose clearance by amounts ranging from 25 to 130 per cent, and averaging 74 per cent. Since these data may be of value in the interpretation of the widely used creatinine clearance tests, and since they have never been published in detail before, they are presented here in full in Table 13. They show remarkable uniformity in the ratios of the creatinine or urea clearances to the xylose clearance, irrespective of urine volume (above the augmentation limit), and illustrate the degree of constancy of each of these clearances that may be expected under controlled conditions.

In view of all the above observations, the results obtained on man can be interpreted only as indicating that creatinine is secreted here as in the dog and dogfish. In the largest doses of phlorizin administered to man, the creatinine clearance was not significantly depressed.<sup>2</sup> In view of the danger attending the intravenous injection of this drug, no attempt was made to determine whether larger doses would depress the creatinine clearance or not.

#### COMPARISON WITH UREA CLEARANCE

There is an evident constancy in the ratio of the urea clearance to the xylose clearance in dogs and in man under various conditions. With few exceptions the urea-xylose ratio in dogs is above 0.5 and usually runs close to 0.7 at moderate to high urine flows (or low U-P ratios) when the urine flow is above the augmentation limit. It may be that some urea is reabsorbed by the tubules after the reabsorption of water has been effected and in consequence of a high concentration gradient between the tubular urine and the plasma, as Rehberg<sup>11</sup> has suggested, but this appears to be an inadequate explanation of the fact that the urea clearance remains persistently at a level of about 70 per cent of the xylose or sucrose clearance at all urine flows above the augmentation limit. In the absence of direct experimental evidence it is futile, however, to speculate upon possible explanations for this phenomenon.

#### CLINICAL APPLICATIONS OF CLEARANCE OF NON-METABOLIZED SUGARS

The introduction of the urea clearance test (Austin, Stillman and Van Slyke,<sup>1</sup> Moller, McIntosh and Van Slyke<sup>12</sup>) appears to the author to be the most valuable practical contribution made to renal physiology in recent years. Although the discrepancy between the urea clearance and these other clearances cannot be explained at this time, he can see no reason for supplanting the urea-clearance test at this moment in the usual clinical investigations. Apart

from any theoretical uncertainties attached to the use of non metabolized sugars the technical difficulties of determining these substances accurately in plasma and urine offset for the most part any clinical advantage that might be gained from them. It should be pointed out therefore that the laboratory of the Department of Physiology of New York University has never recommended the non metabolized sugars for routine diagnostic purposes.

**Summary**—1 In widely separated animals—the dogfish the dog and man—the non metabolized sugars xylose and sucrose are excreted by the kidneys apparently as indifferent substances. They have been shown to be completely filtrable from the plasma in simultaneous experiments in normal animals they have identical clearances and in the phlorizinized animal the glucose clearance is brought up to the xylose or sucrose clearance without ever significantly exceeding the latter. In the dog xylose sucrose and raffinose are excreted in simultaneous experiments at the same rate of clearance. In view of these facts and the further fact that the

that the rate of their excretion relative to the plasma level may be taken as a measure of the rate of glomerular filtration.

2 In the dogfish the dog and man the creatinine clearance normally exceeds the xylose or sucrose clearance by a variable but always significant amount. In the dogfish this excessive clearance of creatinine amounts to several hundred per cent of the sugar clearance in man 70 to 120 per cent and in the dog 30 to 50 per cent. After the administration of phlorizin to the dog the simultaneous creatinine glucose xylose or sucrose clearances become equal and in the dogfish the creatinine clearance is reduced nearly to the level of the other substances. As a rule this results from a fall in the creatinine clearance rather than from a rise in the xylose or sucrose clearance. The above facts are interpreted to indicate that creatinine is excreted by tubular secretion in addition to glomerular filtration.

3 In the dogfish the tubular clearance of creatinine is related to the plasma level of this substance the clearance falling as the plasma level is increased. This result is consonant with the supposition that the energy available for the secretion of creatinine is constant.

4 In the dog the inorganic phosphate clearance is related to the plasma level of this substance in such a manner that as the latter is increased by the injection of phosphate the clearance rises

investigations carried out in this laboratory. He wishes to express his appreciation of the assistance of Herbert Chasis, Robert W. Clarke, Norman Jolliffe, Robert F. Pitts and James A. Shannon in the preparation of the manuscript.

He also wishes to express his thanks to the editors for their invitation to participate in this volume.

**ADDENDUM** Since this article was prepared, study of the renal excretion of the polysaccharide inulin (mol. wt., 972 or greater) has shown that it is excreted in the urine in the form of a complex with albumin (Westfall and Westfall, 1930).

Both groups have found that inulin is not excreted by the glomerular kidney, and that in normal dogs inulin clearance, at moderate or high rates of urine flow, is approximately the same as that of creatinine, and significantly greater than that of xylose. In addition the New York University investigators find a similar dis-

if xylose (or sucrose) is reabsorbed either actively or passively, the use of these substances for the measurement of glomerular filtration is, of course, invalidated by so much.

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## CHAPTER VI

### THE RÔLE OF THE TUBULES IN THE RENAL EXCRETION OF WATER

By H. L. WHITE, M.D.

**Introduction** —The volume of urine may conceivably be varied in three ways — by variations in the volume of glomerular fluid, by fluctuations in the volume secreted by the tubules, and by alterations in the volume reabsorbed by the tubules. The various mechanisms by which glomerular output may be varied, such as changes in the colloidal osmotic pressure of the plasma in glomerular capillary

at present most workers actively engaged in glomerular physiology are agreed that glomerular function is very probably a passive process. Since there is no convincing evidence that the tubules secrete any significant amount of water this possibility will also not be considered. This chapter will therefore concern itself with the last of these three factors, the role of the reabsorptive function of the tubules in effecting variations in the urinary output of water.

#### DIRECT EVIDENCE OF TUBULAR REABSORPTION

**Observations on the Amphibian Kidney** —Bieter and Hirschfelder<sup>1</sup> believe that a considerable reabsorption of water occurs in the frog's tubule, since a dye color deepens during passage down the tubule. They felt that this deepening could not be due to

thus not proved to be due to water reabsorption unless we accept tubular secretion of fuchsin red as disproved. Richards and Walker<sup>24</sup>



find a definite deepening of color in about the middle third of a blocked tubule into which phenol red has been injected *via* the capsule. This is obviously due to reabsorption of water.

When, however, the tubule is unobstructed and the passage of dye solution not unduly delayed, the evidence for water reabsorption is less striking. Hayman and Richards<sup>15</sup> report a precipitate of various intracapsularly injected dyes as they pass down the tubule but apparently did not consistently see any striking deepening of color. One might raise the point that the observed precipitation might be due to variations in the salt content of the medium as it passes down the tubule rather than to an abstraction of water but this suggestion is of no great value without more information on both the solubilities of the dyes as affected by salts and on the composition of the tubular fluid. In a number of instances Hayman and Richards report that the color produced by glomerular fluid after subcutaneous injection of the dye or chromogen was of about the same intensity as that produced by bladder urine indicating little or no tubular reabsorption of water. In the author's experience (unpublished) with both the frog and *Necturus* a deepening of color as an intracapsularly injected dye solution passes down an unobstructed tubule has been observed at times but is not at all a consistent finding although with the tubule obstructed just below the capsule it is a very striking phenomenon particularly in the frog. Bieter<sup>4</sup> finds evidence of water reabsorption by an obstructed tubule which is diminished by HgCl<sub>2</sub> the solutions being introduced *via* the ureter. Richards<sup>3</sup> had found that the HgCl<sub>2</sub>-damaged tubule may carry out an even more complete reabsorption of the glomerular product than the normal tubule.

fluid moved passively in the cyanide kidney may be as great as that actively reabsorbed in the normal kidney. This assumption can at present be neither proved nor disproved because of lack of information on the pressure in the peritubular capillaries although it may be pointed out that earlier in the same paper (pp. 86-87) Richards and Barnwell suggested that the pressure within the tubular capillaries was probably high enough to overcome the osmotic pressure of the plasma proteins and force some water out. Leaving as unsettled for the present the question of whether tubular capillary pressure or plasma osmotic pressure preponderates (and recognizing that the equilibrium may possibly be shifted in either direction)

the attitude seems reasonable that, while the failure of cyanide to cause marked diuresis in the frog is presumptive evidence that the volume of glomerular fluid does not greatly exceed that of the bladder urine, it is not convincing proof.

The strongest argument in favor of a marked reabsorptive capacity by the plasma proteins through a damaged tubular wall is Richards' observation that anuria may exist with normal or increased rate of glomerular filtration. The possibility that the tubular lumen may have been obstructed by swollen epithelium does not, however appear to have been excluded, this would not interfere with collection by capsular puncture. Richards and Barnwell's observation that dye may be concentrated in the tubules of an excised kidney by tubular reabsorption of water, is again an example of allowing a long time for such a reabsorptive process to operate as is also their observation that phenol solution which had entered the tubular lumen by glomerular filtration from an arterial perfusate becomes concentrated within sixteen minutes after arterial perfusion being continued. Richards and Barnwell feel that the high rates of collection of glomerular fluid which are possible in the frog amount to proof that the total volume greatly exceeds the volume of bladder urine. Richards states that there is good reason for believing that more than 90 per cent of the water of the glomerular filtrate is taken from the lumen of the tubule back into the blood.

The arguments for this stand appear well nigh overwhelming at a rate of 1 c.c. of glomerular fluid per hour with 7000 glomeruli in the two kidneys of a 50-gm frog we have 7 cc. of glomerular fluid per hour. This is certainly more than a frog normally puts out, Koloph's average of 1.3 per cent of body weight per hour would give 0.65 cc. of bladder urine per hour. Richards' calculation leads to a comparable conclusion. At the same time it is very probable that the rate of 1 c.c. per hour is considerably greater than the average for all glomeruli. In naturally select is an answer to this question which would presumably subject the kidney to some influence which would presumably arouse all of the glomeruli to their maximum activity and collect from what appears to be an average capsule rather than from one of the best urine from a cannulated ureter would be collected during the same period and the number of glomeruli afterward determined. The size of the particular glomerulus used could be determined in the sections to check up on how nearly average it was in that respect.

White found that the intracapsular pressure in *Necturus*, calculated on the assumption that all the glomerular fluid traversed the entire length of the tubule, agreed well with the observed intra-

capsular pressure indicating that the volume of fluid was not greatly changed in passing down the tubule. It was realized however, that reabsorption in the lower part of the tubule might not be recognized by this method.

To summarize the evidence from microscopic observation of the amphibian kidney it may be stated positively that a considerable proportion of water can be reabsorbed from the tubular lumen if its stay in the tubule is prolonged. The evidence is less certain but may be tentatively accepted that a considerable fraction of the fluid is reabsorbed during a normal passage.

### INDIRECT EVIDENCE OF TUBULAR REABSORPTION

**Evidence From the Amphibian Kidney**—Reports from Hober's laboratory (Scheminzy<sup>35</sup>) show increases of urine volume of from 50 to 100 per cent following narcosis or asphyxia of the frog's tubules. Oliver and Shevsky<sup>37</sup> found the water output of the winter frog's kidney increased about 250 per cent occasionally more by narcosis or damage of the tubules. While they cite no experiments on tubular narcosis with summer frogs the inference is that there would be little or no increase since they state that with tubular narcosis the water output of the winter frog rises to the normal for a summer frog. Both of these reports are on perfusion experiments with a protein free perfusate and therefore do not conflict with Richards and Barnwell's explanation of the failure of tubular damage to cause diuresis when the kidney is supplied with blood. Miyamura<sup>34, 35</sup> finds that if the renal portal veins in an intact frog or toad are ligated greatly reducing the tubular circulation the output of water is unchanged in summer frogs or toads well supplied with water increased in dry summer animals and in winter animals the increase being more pronounced with dry than with moist animals. This seems best interpreted by the view that the amphibian tubule may or may not reabsorb water according to the organism's need. It follows that while renal portal ligation depresses

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asphyxial agent and glomeruli with normal blood instead of using a protein free perfusate as Scheminzy and Oliver and Shevsky have done. If there is no increase in water output on tubular narcosis of winter frogs kidneys supplied with blood Richards and Barnwell's explanation must be accepted.

So far the author tried merely to answer the question whether or not and to what extent the amphibian tubule reabsorbs water, to him it appears most probable that a significant amount of reabsorption may or may not occur, depending upon existing conditions.

Until the question of water reabsorption by the "normal" amphibian tubule is definitely answered investigations designed to influence such reabsorption by deliberate changes in salt drug or hormone content of the medium would appear premature. A number of such investigations have been carried out only a few can be mentioned. Kusakari and Takeda<sup>20</sup> find that adrenalin and atropine decrease the water output of the perfused summer toad's kidney (protein free perfusate). This is in part due to their vasoconstrictor

hum increasing the latter's avidity for and reabsorption of water. Pilocarpine has the opposite effect on the tubules over and above its vasodilator action. The question of glomerular penetration by renal portal perfusate must always be borne in mind in interpreting such experiments. The authors believe they have excluded this, they used perfusing pressures of 24 and 7 cm. H<sub>2</sub>O for arterial and renal portal perfusions respectively and observed no change in rate of arterial perfusion when adrenalin was added to the renal portal perfusate. While this may not be universally accepted as an adequate criterion the increasing recognition of a need for controls on glomerular penetration by renal portal perfusates raises the hope that the existing confusion in this type of work may some day be cleared up.

**Evidence on Reabsorption by the Mammalian Tubule** - Measurements of glomerular filtration. Limitation of space as well as dearth of real information precludes a satisfactory discussion of the rôle played by the mammalian tubule in regulating the output of water. Since the primary question of the relation between hourly glomerular output and hourly urine volume cannot be answered with certainty one obviously cannot discuss intelligently the effect of drugs hormones etc. on this relation. Two courses

are available. One is to assume that the rate of glomerular output is constant and to ascribe any observed changes in urinary volume to changes in tubular reabsorption. A vast number of reports falling into each of these two general groups is extant. The simplicity of the former conception and one's ability upon its basis to calculate the amounts and percentages of reabsorbed solids as well as of water make a strong appeal. While its applicability has been obvious since Cohn<sup>21</sup> enumerated the concept of non-threshold substances it remained for Rehberg to apply it to a wide variety of physiological and pathological conditions and to state formally the principle of passive backdiffusion. Holten and Reh-

Berg<sup>17</sup> find that the hyposthenuria and polyuria of Bright's disease are probably due to diminished tubular reabsorption of water. Uremic symptoms disappear quickly when the volume of filtrate is well maintained slowly when it is small and they persist when it is greatly decreased. In glomerulonephritis renal arteriosclerosis and amyloid disease the volume of filtrate is reduced the amount of reduction depending on the gravity of the case. Considerable glomerular damage may exist with but little impairment of tubular reabsorptive power although the latter may also be impaired in true glomerulonephritis. Wischegorodzena<sup>18</sup> finds that the oliguria of nephrosis is due to increased tubular reabsorption the glomerular filtration rate remaining normal while in nephritis filtration is diminished and reabsorption may be diuresis of diabetes insipidus is due to decreased reabsorption. Most of Wischegorodzena's work was done contrary to Rehberg's specifications without having raised the plasma creatinine level. It is interesting to note that he finds values for filtration rates comparable with those obtained by Rehberg. Since as Peters and Van Slyke<sup>19</sup> say about the chromogenic substance spontaneously occurring in the plasma it is uncertain what the substance thus calculated as creatinine is except that it is not creatinine. Results are of questionable significance. As and Rehberg<sup>20</sup> find that the increase in urine volume in the recumbent is compared with the standing posture is accompanied by a decrease in the protein content and colloidal osmotic pressure of the plasma and by an increase in filtration rate. There may also be a decrease in tubular reabsorption in recumbency but this is not invariable. The fact that one may not accept the premises upon which this work is based and may choose to substitute tubular secretion of creatinine for Rehberg's rate of glomerular filtration while it detracts from its theoretical significance does not invalidate it as a practical diagnostic and prognostic procedure. The probability that this concept actually rests upon a sound theoretical basis is supported by the finding of Poulson<sup>21</sup> that a close parallelism exists between the concentration ratios of glucose (under phlorhizin) and creatinine although the ratios were not identical. Although he did not determine plasma sulphates Poulson<sup>22</sup> further found that when the urinary concentration of inorganic sulphate is plotted against the concentration ratio of creatinine the points fall reasonably well on a straight line. He considered this as evidence that sulphate is concentrated to about the same extent as creatinine. The inadequacy of this evidence is shown by the findings of Haysman and Johnston<sup>14</sup> of Cope<sup>15</sup> and of White and Monaghan<sup>17</sup> that the clearance (urine content / plasma content  $\times$  urine volume) of inorganic sulphate is much less than that of creatinine.

Jolliffe Shannon and Smith<sup>13</sup> and Shannon Jolliffe and Smith<sup>14</sup> report that the clearances of raffinose of xylose, of sucrose and (under phlorhizin) of glucose are identical and that the clearance of creatinine is in the dog 15 to 40 per cent greater than that of the inert sugars. Jolliffe and Chasis<sup>15</sup> report that in man the clearance of creatinine is about 75 per cent greater than that of xylose. Smith and collaborators conclude that the clearance of any of the inert sugars may be taken as the glomerular filtration rate and that the extra creatinine is secreted by the tubules. White and Monaghan<sup>16</sup> failed to find the almost complete identity of clearances of the various inert sugars reported by Jolliffe Shannon and Smith but do find that they are rarely more than 40 per cent apart. Creatinine clearance is 25 to 90 per cent higher than xylose and 15 to 50 per cent higher than sucrose. They feel that creatinine or (under phlorhizin) glucose clearances are a better measure of glomerular filtration than xylose or sucrose. Regardless of whether the creatinine or the xylose sucrose clearance is taken, the glomerular filtrate so calculated is many times the volume of urine, from 10 to 200 times depending on the rate of urine flow. Shannon Jolliffe and Smith and White and Monaghan as well as earlier workers find that the creatinine clearance is not influenced by the plasma creatinine level or by a water diuresis. The clearances of the sugars referred to above are also independent of the plasma levels and water outputs even if these clearances are not a quantitative measure of filtrate volume it is at least probable that they are proportional to it.

The other course referred to at the beginning of this section yields results more difficult of interpretation although certain conclusions can be definitely stated. Thus an intravenous injection of a strongly hypertonic salt solution may increase the urine flow fiftyfold above the resting level. This to be sure is probably due in part to an increase in glomerular filtrate but it is beyond all probability that the volume of filtrate is increased to any such

osmotic resistance to the passage of water from lumen to cell. In other cases however as with drinking water the mechanism is less evident.

Various attempts have been made to distinguish between the glomerular and tubular roles in regulating renal output of water in the mammal none with complete success. Such procedures as excision of the renal medulla asphyxia and the use of poisons or narcotics designed to act selectively on the tubules have been employed. Thus Starling and Verney<sup>17</sup> found a considerable increase in urine flow on adding cyanide to the blood of a heart-

lung kidney preparation, this being ascribed to an abolition of tubular function. MacNider<sup>27</sup> found a persistent polyuria in the chronic nephritis of uranium nitrate in dogs, the lesions being confined largely to the proximal convoluted tubule. There seems to be no question, on the basis of experiments other than those purporting to measure glomerular filtration-rate, that mammalian tubules reabsorb a large part of the glomerular filtrate.

**The Effect of Drinking Water on the Tubular Reabsorption of Water** — Many papers on water diuresis have appeared but no quantitative conclusions on the relative roles played by glomeruli and tubules can be drawn unless one accepts the clearance of some substance as creatinine or inert sugar, as a measure of glomerular filtration. Examinations of the plasma with respect to changes in electrolytes, protein and total solid content, plasma volume, colloidal osmotic pressure, etc. have been carried out but no conclusive explanation of the processes involved has appeared. Riach<sup>27</sup> found that isotonic saline by mouth constantly produced in unanesthetized dogs a low delayed diuresis with a slight increase in serum electrolytes and a considerable dilution of total solids. With water there were a constant but very variable dilution of total solids and a constant slight dilution of electrolytes. The diuretic response always lagged from fifteen to twenty minutes behind the serum changes. Smirk<sup>28</sup> found that following either water or isotonic NaCl solution by mouth in unanesthetized rabbits there were usually a dilution of hemoglobin, of blood total solids and of plasma total nitrogen and a reduction in percentage cell volume but there was no correlation between the extent of the dilution and the degree of diuresis.

Heller and Smirk<sup>18</sup> in a series of papers report a large number of observations among which are that in the guinea pig and rat the tissue load of absorbed but unexcreted water reaches a maximum from twenty to forty minutes before the maximum diuresis, but that in the rabbit alimentary absorption is not much in advance of excretion, that the rate of urine flow is not proportional to the existing water load, that the diuretic response of rabbits to a given dose of water is less in a warm than in a cool environment but that this is not primarily due to the increased extrarenal water loss

depend upon an excess of water in the tissues but may be partly

<sup>1</sup> pitressin which as has long been known, greatly reduces diuretic response to water, that pitressin does not retard the ali-

mentary absorption of water, and, finally, that in rats alimentary absorption of water is delayed and diuresis inhibited by ether and chloroform, but that the inhibition of diuresis persists even when the water absorption is allowed to take place before the anesthesia. A delay in diuresis was confirmed by Klsiecki, Pickford, Rothschild and Verney,<sup>50</sup> who found that the peak of the tissue water load in unanesthetized dogs after 250 cc of water by stomach tube preceded the peak of urine flow by fifteen minutes, the water load had fallen to 75 per cent of maximum by the time the urine flow had reached maximum. Denervation of one or both kidneys does not influence the response. The water diuresis is inhibited by exercise, this is not due to any diminution in absorption from the intestines and it occurs with a denervated kidney as with a normal. Diminished urine flow is accompanied by a rise in urine chloride concentration. The inhibition of diuresis by postpituitary extract is the same with a denervated as with a normal kidney, there is no diminution in intestinal absorption.

All the evidence favors the view that the diuresis from drinking water depends upon a diminished tubular reabsorption rather than an increased glomerular filtration. This view is confirmed by clearance measurements of creatinine and inert sugars. What the

if the injection is made at such a rate as not to produce much hemolysis. The view that increase in water content in plasma acts directly on the kidney cells fails, as Verney and collaborators<sup>50a</sup> point out to explain other very similar polyurias, *i e.*, those of diabetes insipidus, hypophysectomy, piqure and of the isolated mammalian kidney, in none of which is there an increase in water content of plasma, but rather a decrease. There is with the above-mentioned polyurias a deficit of postpituitary secretion and the polyuria is abolished by the secretion. Verney believes that water diuresis is brought about by a diminution or abolition of the secretion by the posterior pituitary of a hormone which maintains the normal capacity of the tubular cells to reabsorb water. When the

mediation of the nervous system, by the concentration of water in blood and tissues, being diminished by an excess of water. The lag in the diuretic response behind the water load is assumed to be due to the time required for the disappearance of the preëxisting



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water in the blood to be the mediate stimulus to the kidney in water excretion those who adhere to the hypothesis of Haldane and Priestley (1916) believe it to be the immediate stimulus This concept is considerably weakened by the recent finding of Newton and Smirk <sup>18</sup> that totally hypophysectomized decerebrate cats show the same lag of diuresis behind water load as do normals Similar experiments on diabetes insipidus patients might be worth while

Fremont Smith and collaborators <sup>2</sup> found no significant serum dilution or change in creatinine clearance during the diuresis of water-drinking in normal human subjects In edematous or febrile subjects or after pituitrin injection the diuresis was abolished or delayed and serum dilution occurred They explain the diuresis without increase in creatinine clearance (considered a measure of glomerular filtrate) by the assumption that in this diuresis the total

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correspondingly shorter time available for tubular reabsorption There is thus a smaller percentage tubular reabsorption not because of an actual lessening of the reabsorptive function of the tubules but merely because the opportunity for reabsorption is diminished Recognizing that any statement on this topic must be one of opinion rather than of demonstrated fact it seems to the author more

time for the reabsorptive process to be carried out

**The Effect of Salts and Acids on the Renal Output of Water**—An adequate discussion of this topic will not be attempted since we are trying to confine ourselves to the tubules A large amount of information exists on the kidney's response to varying intakes of water salts and acids and the changes in water output are very probably due primarily to changes in the extent of tubular reabsorption but an unqualified differentiation between the glomerular and tubular roles cannot be made The papers of Adolph <sup>12</sup> White <sup>13</sup> and Hansen Fosdick and Dragstedt <sup>14</sup> may be cited Chabamer Lobo Onell and Lefu <sup>9</sup> followed plasma Na and Cl and urine Na Cl and pH before during and after the administration of water iso tonic and hypertonic NaCl solutions insulin and a mercurial diuretic neptal Their findings which are not new, are (1) That an increased water output shifts the urine toward alkalinity and *vice versa* (2) that the pH of the tubular epithelium changes in the

direction opposite to that of the urine anions being attracted to the epithelial cells when cations are in excess in urine, and *vice versa*. Differences in the plasma salt content on water, salt and natrial diuresis are discussed but the details cannot be considered here, suffice it to say that the results cannot be explained on the basis of these changes without postulating a variability of the tubular cells reaction to their environment. The increased basicity of the urine on diuresis is explained as due to a shift in the isoelectric point perhaps hormonally produced of the tubule cells. This would mean according to the reabsorption view that on diuresis the isoelectric point shifts toward the alkaline side the protoplasmic cations. The tubular secretion of the facts. An

increased avidity of the cells for cations would explain the latter removal from the blood stream but the process must be reversible to permit their liberation into the tubular lumen. The required postulates become very complex as one tries to explain the differences in the salt outputs of water salt and natrial diuresis two sets of cellular proteins being required whose isoelectric points shift reversibly in opposite directions. Tantastic as these considerations may seem it has long been obvious to workers interested primarily in the mechanisms rather than the end results of cellular activities that some such process or processes must be operative although the mechanism is obscure. This type of conception assigns to the tubules the major role in effecting fluctuations of urinary water output. Keller<sup>40</sup> believes that to a large extent the tubular reabsorption of water and other constituents is explained by their electrical charges with respect to those of the cells. Among other examples are the reabsorption of positively charged water by the negatively charged protoplasm of the proximal tubule cells, acid diminishes the negative charge of the cell constituents concerned thereby diminishing the reabsorption of water. The reabsorption of the negatively charged glucose is assigned to certain cell constituents shown by staining reactions to be positively charged. He cites Glickhorn's demonstration that the zone of tubule stained by acid (negative) dyestuffs is increased by decreasing the pH of the environment.

**Further Consideration of Drugs and Hormones** —Bieter<sup>4</sup> finds that

of the urine so obtained is the same as that of the caffeine urine indicating that the effect was primarily glomerular. However some of the work on creatinine clearance, mentioned below, favors the view that xanthin derivatives also influence tubular reabsorption of water. Richards and Schmidt showed that small doses of pituitrin may increase glomerular circulation while large doses may decrease it. If however, clearance of creatinine or of inert sugar is considered as a measure of or proportional to the glomerular filtrate the findings of Poulsson<sup>20</sup> and of Burgess, Harvey and Marshall<sup>7</sup> indicate no change in glomerular filtration during the antidiuretic action of pituitrin in the mammal. The latter workers found further that pituitary extract is antidiuretic in the bird and reptile but not in the amphibian or fish that the antidiuretic action in the bird is sometimes but not necessarily accompanied by a decrease in glomerular filtration as measured by inert sugar clearance and that in the reptile the glomerular filtrate is very greatly reduced by pituitrin. The antidiuretic effect in the mammal or bird is ascribed to an increased water reabsorption by the thin segment of the loop of Henle. The fish and amphibian have no loop and do not exhibit the antidiuretic response. The reptile also lacks a loop of Henle but the antidiuretic response is apparently due to a great reduction in glomerular filtration which effect is not observed in the bird. It seems most probable that the antidiuretic effect of pituitrin in normal mammals is due to an increase in glomerular filtration and in diabetes insipidus is best explained by assigning to the hormone the ability to increase the tubular reabsorption of water.

Verney and collaborators<sup>20a</sup> find that thyroxin subcutaneously opposes pituitrin and it increases the intensity and shortens the duration of water diuresis. Silvette and Britton<sup>21</sup> showed that adrenalectomized rats give a lower diuretic response to intra peritoneally injected water or aqueous solutions than do normal rats. The response of adrenalectomized rats was restored to normal on the administration of adrenal cortex extract but the extract did not influence the response of normal rats. The water content of the tissues of adrenalectomized rats is greater than normal, in adrenalectomized cats the water content of certain tissues as liver and skeletal muscle is increased that of the blood and kidneys is decreased and that of the skin spleen and brain unchanged. It is concluded that the diminished ability of adrenalectomized animals

according to their findings and to the fact that osmotic diuretics, such as mannitol, glycerol, urea, and sodium sulfate, produce tubular diuresis. Schmitz<sup>22</sup> finds no change in creatinine clearance with an organic mercurial (salyrgan) diuresis but finds an increase

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on a xanthin (caphyllin) diuresis he also found an increased creatinine clearance on the diuresis of intravenous injections of isotonic NaCl solution. However Luggett and Grant<sup>11</sup> found no change in creatinine clearance in the diuresis produced by small doses of NaCl intravenously. If this clearance is considered a quantitative measure of or even proportional to the rate of glomerular filtration it is thus seen that there is a disagreement not of interpretation but in the experimental findings on whether diureses discussed in this section are primarily glomerular or tubular. The matter must be regarded as still unsettled. It is quite possible that in some cases as with xanthin derivatives there is both increase in glomerular filtration and a decrease in tubular reabsorption, the author's personal belief is that the latter is the important

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## CHAPTER VII

### THE EFFECT OF THE SPLANCHNICS UPON GLOMERULAR BLOOD FLOW \*

By RAYMOND A. BIETER, M.D., PH.D.

**Introduction**—Claude Bernard in 1859 published his findings on the nerve supply of the kidney. He was a contemporary of the early triumvirate of kidney physiologists Bowman, Ludwig and Isaacs whose publications in 1812, 1844 and 1857 respectively ushered in the modern era of kidney physiology.

Bernard sectioned the splanchnics in dogs and rabbits and noted that the secretion of urine was increased. When the peripheral ends of these nerves were stimulated the secretion of urine stopped and was not resumed during the period of excitation. Section of the vagus and stimulation of its peripheral end produced no change in the flow of urine. On the stimulation of the central end of the cut vagus he obtained a decrease in the urine output. He also observed that section of the spinal cord stopped the secretion of urine but if artificial respiration was administered the urine flow began again. In a curarized animal first without respiratory movements and then with artificial respiration he obtained similar results.

Bernard from his experiments was greatly impressed with the regulatory role upon kidney activity exercised by the renal nerves by means of their control of the capillary circulation. It is interesting in the light of modern work that Bernard conceived the idea of functional intermittency.

From Bernard down to the present section of the splanchnics has repeatedly been observed to increase the flow of urine. To the results obtained by splanchnic section might be added the findings of investigators who have reported increased urine output from transplanted kidneys principally in the case of autogenous transplants the diuresis lasting at least some days following the operative procedure. Here the results have to do with kidneys deprived of their entire nerve supply. These investigators are of the opinion that life is compatible with complete denervation of the kidneys and cite experiments of animals living a normal life with a single denervated kidney for as long as six years (*Auer<sup>24</sup>*).

\* Abstract of Bieter, R. N., 1930. The effects of the splanchnics upon glomerular blood flow in the frog's kidney. *Am. J. Phys.* 91: 436-454.

Cohnheim and Roy\* were the first to study the effect of the splanchnic nerve upon kidney volume and blood flow with a technique capable of rendering satisfactory results. They were the first to use the oncometer to study changes in kidney volume. From a series of varied experiments including the section of the splanchnics they were able to show that contrary to their expectation section of the splanchnics did not produce a definite increase in kidney volume while stimulation of the peripheral ends caused marked contraction as well as rise in blood pressure. Similar reflex contraction was obtained by central stimulation of cut nerves like the sciatic and vagus. In contradistinction to these results experiments upon the completely denervated kidney showed this to increase in size with rise of blood pressure and decrease with fall of pressure. Bradford<sup>1</sup> demonstrated vasoconstriction within the kidney and resulting shrinkage and vasodilatation with expansion of the kidney. From rapid electric stimulation of the posterior roots of the spinal cord Bradford obtained marked constriction of the kidney. He obtained this effect with roots beginning with the sixth dorsal and terminating in the second lumbar the most marked effect being obtained from stimulation of the roots from the tenth to the thirteenth dorsals. Using a similar stimulus but with a different rate of one or two stimulations per second only on the same cut roots he obtained dilatation of the kidney. Applying these different rates of stimulation to the splanchnic nerves he obtained the same results. Applying them to the peripheral end of the divided vagus Bradford like Cohnheim and Roy obtained no effect on the kidney. Stimulating the central ends of divided sensory nerves such as the sciatic vagus and intercostal he confirmed Cohnheim and Roy in finding reflex contraction of the kidney. Thus it was proven that as far as blood vessel effects are concerned the kidney is an organ well supplied with vasoconstrictors and, to a lesser extent with vasodilators.

Another important contribution was added when it was shown by Burton-Opitz and Lucas<sup>2</sup> that section of the splanchnics increases the blood flow through the kidneys whereas stimulation of the splanchnics decreases the flow. Later Burton-Opitz showed that the right and left splanchnics were distributed to the right and left kidneys respectively.

Thus section of the splanchnics which removes their influence results in an increase in urine output whereas stimulation of their peripheral ends which leads to an increase in their function results in a decrease in urine output. We associate with this the findings that section of the splanchnics increases the blood flow through the kidney whereas peripheral stimulation decreases the renal blood flow. Modern kidney physiology now raises the question: What part is played by the glomerulus in these variations of function?



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From Bernard down to the present section of the splanchnics has repeatedly been observed to increase the flow of urine. To the results obtained by splanchnic section might be added the findings of investigators who have reported increased urine output from transplanted kidneys principally in the case of autogenous transplants the diuresis lasting at least some days following the operative procedure. Here the results have to do with kidneys deprived of their entire nerve supply. These investigators are of the opinion that life is compatible with complete denervation of the kidneys and cite experiments of animals living a normal life with a single denervated kidney for as long as six years (Zavjer<sup>24</sup>).

\* Abstract of Bieter R. N. 1930. The effects of the splanchnics upon glomerular blood flow in the frog's kidney. *Am. J. Phys.* 91: 476-485.

Cohnheim and Roy<sup>9</sup> were the first to study the effect of the splanchnic nerve upon kidney volume and blood flow with a technique capable of rendering satisfactory results. They were the first to use the oncometer to study changes in kidney volume. From a series of varied experiments including the section of the splanchnics they were able to show that contrary to their expectation section of the splanchnics did not produce a definite increase in kidney volume while stimulation of the peripheral ends caused marked contraction as well as rise in blood pressure. Similar reflex contraction was obtained by central stimulation of cut nerves like the sciatic and vagus. In contradistinction to these results experiments upon the completely denervated kidney showed this to increase in size with rise of blood pressure and decrease with fall of pressure. Bradford<sup>8</sup> demonstrated vasoconstriction within the kidney and resulting shrinkage and vasodilatation with expansion of the kidney. From rapid electric stimulation of the posterior roots of the spinal cord Bradford obtained marked constriction of the kidney. He obtained this effect with roots beginning with the sixth dorsal and terminating in the second lumbar the most marked effect being obtained from stimulation of the roots from the tenth to the thirteenth dorsals. Using a similar stimulus but with a different rate of one or two stimulations per second only on the same cut roots he obtained dilatation of the kidney. Applying these different rates of stimulation to the splanchnic nerves he obtained the same results. Applying them to the peripheral end of the divided vagus Bradford like Cohnheim and Roy obtained no effect on the kidney. Stimulating the central ends of divided sensory nerves such as the sciatic vagus and intercostal he confirmed Cohnheim and Roy in finding reflex contraction of the kidney. Thus it was proven that as far as blood vessel effects are concerned the kidney is an organ well supplied with vasoconstrictors and to a lesser extent with vasodilators.

Another important contribution was added when it was shown by Burton Opitz and Lucas<sup>7</sup> that section of the splanchnics increases the blood flow through the kidneys whereas stimulation of the splanchnics decreases the flow. Later Burton-Opitz showed that the right and left splanchnics were distributed to the right and left kidneys respectively.

Thus section of the splanchnics which removes their influence results in an increase in urine output whereas stimulation of their peripheral ends which leads to an increase in their function results

part is played by the glomerulus in these variations of function?

Richards and Schmidt<sup>21</sup> and Richards<sup>9</sup> observed that stimulation of the sympathetic fibers to the kidney and stimulation of the central ends of a cut sensory nerve such as the sciatic increased the intermittency of blood flow through the glomeruli. They stated that intermittency of glomerular flow was to be seen even when the brain and spinal cord were destroyed. Among influences which may produce vasodilatation and vasoconstriction in the kidney they counted among the former section of the sympathetic nerve supply to the kidney and among the latter afferent nerve stimulation and direct stimulation of the sympathetic nerve supply to the kidney. They did not present the experimental basis for their pronouncement.

### MICROSCOPIC STUDIES OF GLOMERULAR BLOOD FLOW

The author has studied the effect of electrical stimulation of the sympathetic nerves to the kidney contained in the splanchnics as well as the effect of stimulation of the central ends of cut sensory nerves such as the sciatic and vagus upon the glomerular blood flow in large and small fields of the kidneys of *Rana pipiens* and *Rana catesbeiana*.

**Electrical Stimulation of Splanchnic Sympathetic Nerves** — When a frog was prepared as reported in detail elsewhere the kidney brought into focus with the low power of a microscope and the splanchnic of the same side was stimulated it could be seen as Richards and Schmidt<sup>21</sup> have reported that the blood flow

the more marked was the effect observed. All of the glomeruli did not remain inactive throughout the period of stimulation some resumed flow and in others the flow stopped so that the total number of active and inactive glomeruli showed about the same relationship during the stimulation. Stimulation of both the upper and lower splanchnic trunks was employed. When attention was focused upon one small field (10 experiments) the percentage of arrest was far greater thus in 6 out of 10 recorded experiments on different frogs all of the visible active glomeruli stopped. When the stimulus was discontinued the inactive glomeruli resumed flow within two minutes. In the case of some glomeruli it has been observed that only after four or five repeated short periods of stimulation with a rest period between each has it been possible to stop blood flow. Other glomeruli have been stopped two four six eight and ten times by so many successive stimulations without any apparent difference in their response and return to normal.

It has also been noticed during splanchnic stimulation that some fields of kidney tissue become paler than normal appearing as if there is a great vasoconstriction throughout the kidney

The glomeruli that stop as a result of stimulation generally show

where the afferent vessel was visible, this showed a stoppage of flow during the period of stimulation and a gradual emptying of cells into the glomerulus, after which the afferent artery could no longer be seen. This would indicate a point of great constriction away from the glomerulus, probably at the point of its origin, as has been shown by Krogh<sup>14</sup>. When the electrical stimulation was discontinued, the afferent artery would suddenly show a burst of flow, following which the entire glomerulus would burst into activity, or in other cases the capillaries would assume their flow, one by one, over a period of five to ten seconds



FIG. 13.—Diagram of glomeruli from the frog's kidney showing the shunt between afferent and efferent glomerular arterioles. Afferent Afferent glomerular arteriole Efferent Efferent glomerular arteriole (Baker *Am J Physiol*)

glomerular capillary flow, one and occasionally two capillaries remained which, with the afferent and efferent arteries, showed a very rapid flow. When this was observed it was found practically impossible to stop the flow with electrical stimulation. In every kidney studied in this portion of the work one or two and as high

served that the afferent and efferent arterioles in some cases were

injected whereas the glomerular capillaries remained free of the dye. They concluded that a direct loop between these two arterioles within

No attempt has been made to look for them in *Rana pipiens*.

**Stimulation of Sensory Nerves**—Stimulation of the central ends of cut sensory nerves such as the sciatic and vagus produce the same effects (6 experiments). In each type of stimulation the number of active glomeruli was cut roughly in half. One animal showed almost an 80 per cent decrease in the number of active glomeruli—a greater decrease than was obtained in splanchnic stimulation.

glomeruli tend to  
minutes after

flow was fairly close to the previous level. In small fields of active glomeruli where the effect of stimulation could be observed con-

the splanchnics leads to decreased glomerular flow one naturally wonders what section of the splanchnics will produce. This has been determined upon a series of *Rana pipiens* and *Rana catesbiana*. In every kidney studied (13 experiments) and especially in those kidneys

same side. Out of 13 experiments in 8 this has been controlled by counts of the glomeruli in the opposite or normal kidney. During the time of the experiment which has run from one to two hours no marked change in these results have been observed. Intermittency of glomerular blood flow in these experiments has been the exception rather than the rule. The number of active glomeruli after splanchnic section has remained extremely constant up to one and a half hours following the section. Occasionally 1 glomerulus out of 70 to 100 may show arrest of flow but when this has occurred the periods of intermittency generally have been long (five to ten minutes). In many cases the glomeruli which showed arrest of flow were apt to continue this way throughout the time of the experiment.

In 2 frogs (*Rana catesbiana*) where observations were carried on for over three hours several small fields in a kidney in each animal were found where the glomeruli showed intermittency of blood flow after splanchnic section. During the periods of arrest the afferent arterioles also showed arrest of flow and a complete emptying of red cells into the glomerular capillaries.

Most observers have found that kidneys with sectioned splanchnics at first put out urine in amounts increased over the normal but that eventually the urine volume tends to return to normal. If the observations reported here that at some time after splanchnic section the glomeruli tend to show some intermittency of flow, are correct these two types of observations may be correlated. The immediate effects of splanchnic section are to increase the number of active glomeruli and to increase the volume of urine secreted but sooner or later the afferent arteries and glomeruli establish their own intermittency without nerve control and then the urine volume tends to approximate the original normal level.

**Clamping the Ureters**—Reflex anuria is a condition met with both experimentally and clinically. This condition generally arises from some point of excessive stimulation. It has been reported by Loucks and Scott<sup>18</sup> from pulling on the kidney stretching muscles and incising the skin in dogs. It has been reported by clinicians from inserting a ureteral catheter into the ureter and from instilling drugs such as silver nitrate into the ureter and its association with kidney stones and ureteral kinks is well known. Blum<sup>3</sup> reported a case of complete anuria resulting from a surgical procedure in which the ureter was probably caught in a ligature. Because of its importance and because of what we know of the control of the splanchnics on kidney blood flow and urine output it was thought worth while to try the effect of some of the procedures known to produce anuria upon the activity of the glomeruli both with normal innervation and without splanchnic innervation.

Attention should be called to the fact that immediately after a

following work this is probably the result of reflex closure of the afferent glomerular arterioles.

The effect of placing a small bulldog clamp on the ureter was first tried. In every one of 8 experiments the number of active glomeruli dropped giving an average decrease for all of the experiments of about 40 per cent. The clamp was removed immediately after the count following which the number of active glomeruli began to increase. During the next ten to fifteen minutes the glomeruli reached normal levels.

When the splanchnic nerves were cut this decrease in active glomeruli was not observed. In 5 experiments the number of active glomeruli showed no change neither was there any appreciable change in rate of flow or size of glomeruli. Quinby<sup>19</sup> observed that in handling the ureters of denervated kidneys the temporary inhibition of urine flow seen in normal kidneys after handling the ureter did not occur.

bichloride applied to the ureter externally produce the characteristic arrest of glomerular flow. Again this decrease of glomerular flow is absent when the splanchnics are cut.

**Release of Edema Fluid Previously Developed by Ligature of Limb**—Andrews<sup>1</sup> while investigating experimental uremia, noticed that when dogs' legs developed an edema from too tight a ligature, if then the ligature was removed and the leg massaged anuria occurred. Because of this finding rubber binders were placed on the legs of a series of frogs and in twelve to fifteen hours a marked edema was produced. The leg below the ligature was from one-half to again as large as the normal leg. The frog was now prepared for microscopic observation and as soon as the normal counts of glomeruli had been obtained the ligature was removed and the leg massaged gently. In all animals 5 in number this resulted in a marked decrease of active glomeruli and the return to normal was not complete for fifteen to twenty minutes. Here again the effect was removed by section of the splanchnics as shown in another series of 6 animals with unilateral severing of splanchnic innervation. In the normal kidney the active glomeruli were cut down by almost 50 per cent whereas in the kidney without splanchnic innervation no effect upon the number of active glomeruli was produced. Some slowing of the rate of flow was noticed in 2 of the denervated kidneys. It was thought that this might have been due to a lowering of blood-pressure but direct determinations showed that there was no marked lowering of blood-pressure yet this slowing of blood flow was apparent for at least five minutes. The results of the edema experiments on glomerular blood flow again indicate that the splanchnics play a major rôle in their arrest. Massaging of normal legs had no definite effect on the number of active glomeruli.

**Effects of Irritants Injected Into the Ureter and Tubules**—Lastly the reflex effects on glomerular blood flow from irritants such as bichloride of mercury solution injected into the ureter and into the tubules was determined.

Briefly these experiments showed that 1 per cent bichloride of mercury solutions injected into the ureter and collecting ducts produce a decrease of glomerular blood flow of the same order of magnitude as was observed in other positive experiments described above. This retardation was no more marked when, by higher injection pressure (25 cm  $H_2O$ ) the mercury solutions were forced up into the convoluted tubules. When the splanchnics were previously sectioned no retardation was observed.

These experiments gain support from the anatomical work of

Smirnow<sup>22</sup> Studying the kidneys of mammals, including man and frogs this investigator found nerve fibers between the epithelial cells of the tubules collecting duct and ureter. The endings in the tubules because of their similarity to nerve endings in secreting glands he concluded to be secretory whereas those ending in the collecting ducts pelvis and ureter being more simple in structure than the above he concluded to be sensory. In the experiments

The findings here reported upon the function of the splanchnics when stimulated directly or reflexly to decrease glomerular blood flow and in all probability glomerular filtration and the inhibition of this function by local anesthetization of the part stimulated to produce this reflex such as the ureter and by section of the splanchnics are thought to have a clinical bearing. Whereas these results were obtained in the frog it is likely that in the frog the vasomotor control of the kidney vessels is not as highly developed as it is in mammals and man and consequently ascending the scale the effects would possibly be more powerful. Insofar as they are thus able these results are thought to add confirmations (1) To the report of Neuwirt<sup>17</sup> who with procaine anesthesia of the splanchnics in a case of kidney stone colic relieved the pain and produced a resumption of urine secretion (2) to the reports of Hess<sup>11, 12</sup> who performed renal sympathectomy in 5 cases the result of which was an increased output of urine from the operated kidney and (3) To the report of Rowntree<sup>23</sup> who has studied renal sympathectomy in dogs with similar findings preparatory to applying the procedure clinically.

**Conclusions** —Intermittency of glomerular blood flow and intermittency of capillary flow within the glomerulus in the normal frog's kidney as first reported by Richards<sup>19</sup> is again confirmed. Immediately after splanchnic section in the frog this intermittency for the most part disappears. At three hours after splanchnic section in 2 cases this intermittency was again to be seen in several small fields of glomeruli but the rest periods were no longer than thirty seconds. Section of the splanchnics as an acute effect, results in an increase of glomeruli showing active blood flow.

Various measures such as pinching the ureter and applying an irritant locally both externally and internally and edema fluid let into the general circulation result in reflex arrest of glomerular flow. This reflex arrest of glomerular flow is prevented by splanchnic section and by cocaineization of the part stimulated. The reflex



arrest produced by mercuric chloride in the ureter and collecting ducts appears more pronounced than the reflex arrest coming from within the kidney tubules

These experiments show the marked effect of the splanchnics upon glomerular blood flow and as far as they are able tend to explain how local anesthesia and section of renal nerves will produce beneficial results clinically in reflex oliguria and anuria

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## CHAPTER VIII

### THE EFFECTS OF DIETARY DEFICIENCY ON RENAL GROWTH AND STRUCTURE

By C M JACKSON M D LL D

THE lack of sufficient food or of any one or more of the necessary nutritional factors results in a condition of inanition. The various types of inanition are indicated in the following outline:

Inanition	{	A Total (quantitative)	{	1 Complete (no food whatever)		
				2 Incomplete (insufficient nutrient general underfeeding)		
	{	B Partial (qualitative)	{	1 Complete (entire absence)	{	of one or more of the necessary foodstuffs
						{ proteins fats carbohydrates salts vitamins water
				2 Incomplete (insufficient amount)		

The kidneys, among other organs, are somewhat variably affected according to the type of inanition. Under each type of deficiency, the effects have been studied in man and lower animals, both young and adult. These effects may include changes in renal weight and structure gross and microscopic. Some data are also available concerning the renal weight when normal diet is restored.

#### TOTAL (QUANTITATIVE) INANITION

**Effects of Total Inanition.**—So far as known, the effects on the kidneys are similar during total inanition (with no food or water) and when water only is given, so both conditions will be reviewed together. During total inanition renal function and urinary secretion decrease rapidly to a very low level which is somewhat higher in case water intake is permitted. The effects of inanition upon the amount and composition of the urine are reviewed by Morgulis (1923), and will here be given only incidental notice.

**Changes in Weight of the Kidney.**—Cases of simple starvation are rare in man. The best available data are from necropsies during famine or infantile malnutrition although there are frequently complications, especially infections which may affect the kidney. It is, therefore, not surprising to find the kidneys from such cases quite variable in weight. Table 14 shows the average changes in

TABLE 14 — WEIGHT CHANGES IN ORGANS OF ATROPHIC INFANTS (JACKSON 1925)

Average percentage of decrease in the following organs

Organ				
Brain	+25.9	+1.5	-7.7	-12.3
Lungs*	+24.8	-4.8	-20.6	-21.2
Kidneys	+20.5	-5.7	-1.0	-19.4
Spleen	+9.5	-14.9	-20.8	-31.3
Heart	-0.9	-20.9	-14.8	-28.8
Whole body	0.0	-20.9	-31.8	-51.5
Liver	-6.3	-33.8	-23.2	-27.1
Suprarenals	-43.3	-60.5	-55.9	-38.5
Thymus	-71.8	-80.7	-50.8	-82.6

\* Pneumonia cases excluded

relative weight of the kidneys and some other organs from marasmic infants, calculated by comparison with the (estimated) normal weight on various bases. In this series of 30 to 50 cases, the final body weight averaged 20.9 per cent below the maximum weight recorded during life, 31.6 per cent below the normal for body length and 51.5 per cent below the normal for age. The kidneys had lost in weight relatively less than the body, for they averaged 20.5 per cent above the normal for final body weight, 5.7 per cent below normal for maximum body weight, only 1 per cent below normal for body length, but 19.4 per cent below normal for age. In these malnourished children the kidneys had apparently lost in weight relatively more than the brain and perhaps the lungs, but less than any of the other viscera noted.

The data for undernourished human adults justify a similar conclusion. Bean (1925, 1926) found the kidney weights in 4871 hospital necropsy records 15 per cent higher in the well nourished than in the emaciated. In this series as in the malnourished children, the weight of the kidney was depressed relatively less than that of the heart or liver. However atrophy of the renal parenchyma during inanition may be masked by the increased blood content, since vascular (especially venous) congestion is a common occurrence.

For the lower animals, the observations of numerous investigators indicate that here also during starvation the loss in weight of the adult kidney, though variable, usually averages relatively less than the loss for the entire body. In young growing animals, however, the effect on the kidney (as on other organs) varies greatly according to the age and the length or severity of the inanition. This is illustrated by the results of the author's experiments on young rats (Figs 14 and 15). In fetuses which had been stunted by

In rats severely underfed from  
kidneys appeared 90 per cent

above normal, while in rats underfed from birth to ten weeks of age, the kidneys averaged only .38 per cent above normal weight (Stewart). In rats similarly underfed beginning at three weeks of

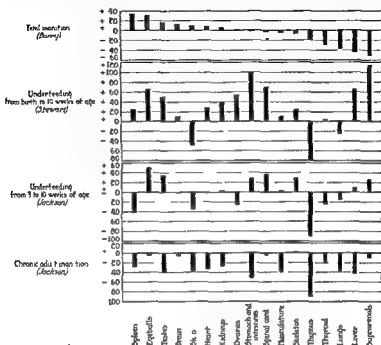


FIG. 14.—Chart showing the average relative (percentage) change in the organ weight.

weight. The kidney weight has lost 27 per cent, or relatively somewhat less than the body weight.

age, the kidneys were only 4 per cent above normal (Jackson). In adult rats subjected to acute or chronic inanition, the kidneys

lost about 26 per cent, while the loss in body weight was 33 to 36 per cent (Jackson)

On the other hand, in fasting adult guinea-pigs, at a loss of 20 per cent in body weight, the kidneys had lost only about 5 per cent (Lazareff). At 35 per cent loss in body weight, the kidneys had lost only about 11 per cent, thus appearing very resistant to inanition. Numerous other data might be cited from various

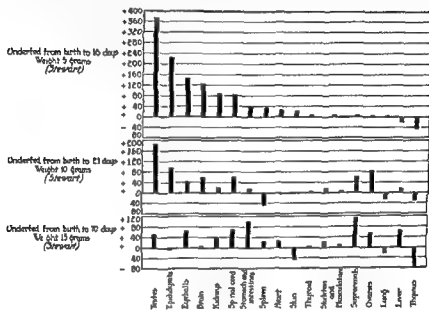


FIG. 15.—Chart showing the average relative (percentage) changes in organ weights

observers on different species, indicating that in general the loss in kidney weight during starvation, though variable, is always relatively less than that of the body.

In albino rats placed on a normal diet after underfeeding from birth or at later periods, Jackson and Stewart found that the kidneys within a few weeks had nearly recovered their normal proportionate weight in most cases though sometimes they remained somewhat above normal.

**Changes in Renal Structure**—The numerous studies dealing with structural changes of the kidney during total inanition have been reviewed in detail by Jackson<sup>2</sup>. The principal results will be summarized briefly. The effects on the kidney, as on other organs, vary considerably according to the species, age and length or severity of the inanition period as well as according to the complications, especially the associated infections.

In general it is found that the earlier stages of inanition may cause practically no structural changes in the kidney, excepting perhaps a slight atrophy of the cytoplasm in the renal epithelial

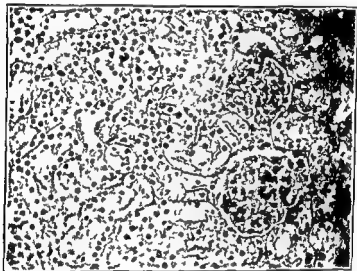


FIG. 16.—From a photograph of a section of the kidney in a normal adult albino rat showing two renal (Malpighian) corpuscles and the adjacent cortical labyrinth chiefly of cortical convoluted tubules. A normal control for comparison with Fig. 17. Zenker fixation, hematoxylin-eosin stain.  $\times 250$ . (Jackson: The Effects of Inanition and Malnutrition. P. Blakiston's Son & Co.)

cells. With more prolonged and severe starvation, the cell atrophy is more pronounced and degenerative changes appear (Figs. 16 and 17). Cloudy swelling is often the earliest observed change, followed by granular and fatty or vacuolar cytoplasmic degeneration. This degeneration affects primarily and especially the epithelium of the convoluted tubules and sometimes Henle's loop. Here, as in other tissues, the nucleus is relatively resistant to inanition so that the earlier cytoplasmic atrophy tends to produce an increased nucleus-plasma ratio. In later stages of degeneration, the nucleus also is involved, showing karyolysis or pyknosis, and, finally, fragmentation (karyorrhexis) associated with the terminal

necrosis and disintegration of the cell. The desquamated cellular debris may form casts which fill some of the tubules. The renal

kidney during inanition is sometimes modified by infections, to which the organism appears predisposed in the generally weakened condition. The blood-borne toxic products from the breakdown of



J. H. 1927

P. Blakiston & Son & Co.)

tissues throughout the body will also necessarily intensify the renal lesions especially in the later stages of inanition.

Jackson<sup>10</sup> has studied the structural changes in new-born rats held at constant body weight for about two weeks by underfeeding. The kidneys have nearly doubled in weight. They show no degen-

genic zone (normally present in new-born rats) has become reduced with mitoses and developing glomeruli.

Relatively few data are available concerning the recovery of normal structure in the kidney through refeeding after a period of total inanition. Morpurgo found that in growing rabbits mitoses in the kidney are suppressed by starvation but reappear in large numbers on refeeding. Kittelson similarly noted that in underfed new born rats the development of new renal corpuscles ceases. On refeeding the renal corpuscles become hypertrophied and increased in number apparently even beyond the normal. During inanition the renal cortex is retarded in growth more than the medulla but the normal proportions are soon restored upon refeeding. In general it appears that especially in the young the renal lesions occasioned by inanition are as a rule promptly healed upon adequate refeeding.

### PARTIAL (QUALITATIVE) INANITION

**Effects of Partial Inanition.** Changes in the kidneys have been noted during dietary deficiencies of protein, fat, mineral salts, water and vitamins. The earlier literature (Jackson<sup>2</sup>) will be summarized briefly and supplemented by the more recent findings.

**Protein Deficiency.** In human famine and allied conditions there is frequently a generalized edema of the body known as "famine edema" or malnutritional edema. While various causes have been suspected the preponderance of evidence including recent experimental work indicates strongly that the most important factor in the pathogenesis of this edema is protein deficiency (Hoelzel, 1928 and others).

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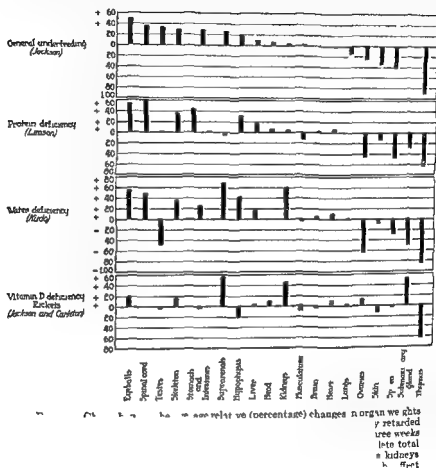
account for the edema. Some data from the Russian famine were reported by Anitschkoff and Swodski (1922).

Frisch, Mendel and Leiter<sup>4</sup> have confirmed Kohman's experimental production of edema in rats by low protein diet but they made no observations on the urinary system. Winters, Smith and Mendel (1927) found an increase of 50 per cent in the renal weight of young rats held forty days on an inadequate protein diet. Wang, Huddleston and Saplar<sup>10</sup> on the contrary found the kidney size proportional to the body size in young rats with arrested or retarded growth on diets deficient in protein. The only change noted in kidney structure was frequent cloudy swelling. Similarly Timson and Jackson<sup>4</sup> found nearly normal kidney weight in young rats held at constant body weight for some months by low protein diet (Fig. 18). No edema was noted in these experiments.

Leiter,<sup>2</sup> Barker<sup>1</sup> and Barker and Kirk<sup>3</sup> have produced a variable edema in dogs by plasmapheresis which lowers the serum protein



directly through repeated bleedings rather than by limiting the protein intake. According to Barker the urine in these dogs shows albumin fat droplets and renal cell remnants. The kidney lesions present a progressive degeneration of the renal tubules



with some destruction of the glomeruli and scar tissue formation. The picture suggests nephritis perhaps due to associated infection similar to that frequently found in various types of inanition.

**Fat Deficiency**—Until quite recently it has generally been assumed that fats can be sufficiently synthesized in the organism,

so that a dietary intake of fat is not essential. Farther unfavorable results on fat free diets were ascribed to shortage of the associated fat-soluble vitamins. McAmis, Anderson and Mendel<sup>12</sup> in rats on extremely low fat but otherwise presumably adequate diets sometimes noted bloody urine, urinary calculi and mottled or pitted kidneys. But eye disorders resembling incipient ophthalmia were also occasionally observed that would indicate the possibility of a vitamin A deficiency in which renal lesions are known to occur. Burr and Burr<sup>13</sup> however working with purified diets adequate except for extremely low fat content discovered a new disorder. This disorder can be prevented or cured by adding small quantities of certain fatty substances including pure fatty acids. The symptoms included a suppression of growth, a peculiar scaliness of the skin and occasional hematuria but no symptoms of deficiency in vitamin A or other known vitamins.

Since the kidneys of Burr's rats at autopsy often appeared grossly abnormal with markedly granular or pitted surfaces a histological study of the series (total of 73 rats) was made by Borland and Jackson.<sup>3</sup> Although the body weight of the test rats was variably subnormal the kidneys typically averaged more than 20 per cent above the Wistar norm. The renal surface was pale and granular, sometimes deeply pitted. Degenerative changes appeared to a variable extent in the renal epithelium, more intensive as a rule in the medulla. Atrophy or fatty metamorphosis of the epithelium was often found in both cortex and medulla. Desquamated and disintegrated cells accumulated to form casts, fatty or non fatty, which often filled some of the tubules and especially the papillary ducts. In many cases the degenerating epithelium and casts were calcified, somewhat resembling the condition described by Van Leersum in vitamin A deficiency (to be considered later). In some cases this calcareous degeneration led to extensive necrosis and destruction of the apical region in the renal medulla (Fig. 19). Especially near such areas of necrosis there was also a marked proliferation of the renal pelvic epithelium forming large irregular masses. This proliferated epithelium however showed no trace of the cornification found in vitamin A deficiency. Slight round-cell (lymphocytic) infiltration occurred in the kidney with about equal frequency in the test rats and apparently normal controls. In only 2 cases polymorphonuclear cells appeared representing a superimposed infection in the markedly necrotic areas.

The addition of 20 per cent of fat (lard) to the diet almost completely prevented or cured these renal lesions. Even much smaller amounts of various fats appeared highly beneficial although in some cases marked renal lesions persisted when the general condition of the body had been apparently restored to normal. Thus

the kidney appears to be somewhat more sensitive than the skin or body in general to the effects of a dietary deficiency in fat.

**Mineral Deficiency**—The only data available concerning the effects of mineral deficiency on the kidney are from the experiments of Schultz<sup>17</sup>. He found that in rats held at constant body weight (45 gm) for forty days on low salt diet the kidneys increased 63 per cent in weight, while in the controls similarly held constant by low calorie diet the kidneys increased only 14 per cent. Sections of the kidney showed no significant changes, although some swollen tubules appeared in both test and control animals.

**Water Deficiency**—The kidneys apparently suffer rather severely from water deficiency, perhaps on account of the associated thicken-

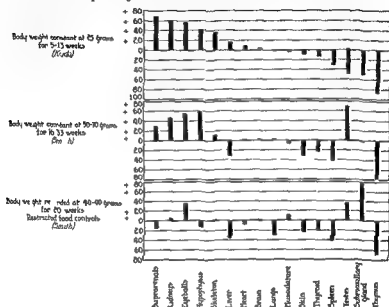


eosin stain (Borland)

ing of the blood, which may impede the circulation. Kudo found that while in adult rats on dry diets the loss in renal weight was similar to that during total inanition, in young rats held at constant weight by dry diets the increase in kidney weight (35 to 65 per cent) was much greater than that during simple underfeeding (Figs 18 and 20). These results were confirmed by Jackson and Smith.<sup>11</sup>

Among the earlier observers, Pernice and Scagliosi found in thirsting animals (dog and chick) intense degenerative lesions involving the glomeruli as well as the renal tubules. Hyperemia was marked and hemorrhages into the capsular space and tubules were frequent. Garofenu and Derevici (1924), in dogs on dry diet, found the glomerular capillaries dilated, with cortical lesions in

advanced cases Kramár<sup>18</sup> and Kramár and Kovács (1927) have made extensive studies of the renal condition in puppies on dry (condensed milk) diet. Symptoms of toxicosis appear with albuminuria glycosuria cylindruria and renal lesions. The renal lesions which are somewhat irregular and inconstant include hyperemia which is greatest among the straight tubules and fatty infiltration especially in the convoluted tubules.



average is only 5 per cent above normal

In children on a relatively dry diet (or dry milk, potato flour, butter and sugar) Schiff and Bayer (1924) found a dehydration pyuria. Mild albuminuria, variable casts, leukocytes and red blood cells appeared in the urine. Renal abscesses may arise through bacteremia, the resistance of the kidneys being reduced by the effects of dehydration. Aron (1926) similarly noted that

the kidneys suffer from water deficiency resulting in oliguria or even anuria with urinary casts and leukocytes. Any existing pyelitis is aggravated.

Since urinary secretion is reduced to a minimum during inanition and especially during thirst it was formerly thought that a study of the finer structure in this condition might throw some light on the much disputed question as to the mechanism of urinary secretion. But this hope has not been realized. From a study of the kidney of bats during hibernation (where likewise urinary secretion is quiescent) Disse concluded that the brush border of the epithelium in the convoluted tubules represents a resting condition and that it disappears during active secretion. Other investigators have failed to confirm this and find no significant change of the brush border during renal secretory inactivity (in hibernation, thirst, etc.) or hyperactivity (experimental diuresis). During the

shown to be related to the process of secretion. The phenomena of the so-called secretion (or resorption) of carmine or other dyes have been studied by Suzuki and others in fasting and thirsting animals but the results are open to different interpretations.

**Vitamin Deficiencies**—It has already been noted that one of the complications of inanition in general is a predisposition to infections in the weakened condition of the organism. This lowered resistance to infections is especially marked as a result of certain vitamin deficiencies. Abels designated this characteristic predisposition to infection during avitaminosis as *dysergy*, the corresponding structural changes being termed *dystrophy*. Both *dysergy* and *dystrophy* are found well marked in the kidney during various vitamin deficiencies.

The effects of vitamin deficiency and of other forms of partial inanition often bear a striking resemblance to those of total inanition. This similarity of effects in all types of inanition may perhaps be ascribed to the common factor of obstruction to nutri-

result of tissue breakdown throughout the body especially in the later stages of inanition. In addition to these more generalized effects however each type of inanition produces its own more specific effects probably representing the peculiar disturbances of metabolism occasioned by the deficiencies of the respective individual nutritional elements.

McLennan and Jackson<sup>6</sup> found that in adult rats fed a diet deficient in calories but containing the normal requirements in

dietary accessories (proteins, salts and vitamins), resulting in a loss of 40 per cent in body weight, the kidneys lost 26 per cent. In another group fed a starch-sugar mixture containing equivalent calories, with the same loss in body weight, the kidneys lost 33 per cent, or about the same as in rats on water alone. Thus the presence of the accessory factors seemed slightly to protect the kidney from loss in weight during inanition.

**Vitamin A Deficiency (Xerophthalmia)** — As an example of dysergy, an epidemic of 'spontaneous' nephritis was observed by Jackson in a colony of rats fed on a cereal mixture apparently deficient in vitamin A. The eyes showed symptoms of xerophthalmia. The kidneys were variable in weight and presented various stages of a focal interstitial nephritis (Figs 21 and 22) with marked round-



FIG. 21.—From a photograph showing the pitted granular surface of an albino rat developing a spontaneous interstitial nephritis on a diet low in vitamin A. The smooth surface of the kidney in a normal rat is shown on the left.

cell (usually lymphocytic) infiltrations. Many renal tubules were

compensatory hypertrophy with weight ultimately doubled or more. This increase (which was much greater than the compensatory hypertrophy of the normal kidney) was due partly to general dilation of the renal tubules (Fig. 23). Similar infective lesions with multiple renal abscesses were found by Frontali in rats with experimental xerophthalmia on diets deficient in vitamin A. A characteristic hyperplasia of the renal pelvic epithelium with more or less cornification, was observed in experimental animals by

Wolbach and Howe Frontali, Fujimaki Van Leersum and Tyson and Smith

One of the most important and striking recent advances in the pathology of nutrition is the demonstration of urolithiasis through vitamin A deficiency. Osborne and Mendel discovered urinary or renal calculi in about 10 per cent of their rats on diet deficient in vitamin A while no calculi were found in the control on normal diet. This result has been abundantly confirmed by Fujimaki and McCarrison especially in rats on diets deficient in other factors in addition to vitamin A. In some cases the vesical calculi (visible by the roentgen rays) disappeared when the animal



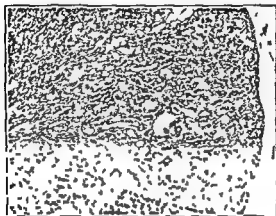
— — — — — of the kidney cortex showing the structure of the renal tubules and ducts

A depression on the renal surface is shown at the right

were placed on normal diet. Similar results were obtained by Van Leersum, Perlmann and Weber, and Tyson and Smith working on vitamin A-free diets.

The work of Van Leersum is of especial interest and importance, because he could find no cystitis but traced the pathogenesis of the calculi to the kidney. In 88 per cent of his test animals, sections showed numerous small calcareo-fatty granular concretions or casts in the renal tubules and ducts. (These somewhat resemble the above-mentioned changes resulting from fat deficiency.) He concluded that degeneration of the renal epithelium caused the calcareous deposits and that these were carried to the bladder, where they grew to form the larger concretions. Recently Tyson and Smith have likewise noted that renal calculi frequently appear

in rats on low vitamin A diets. When obstruction to urinary outflow is present pyonephrosis develops. They conclude that there is no metaplasia of the renal pelvic epithelium without infection which is present from the beginning in all cases. Furthermore this abnormal epithelium with acute or chronic renal infection may persist following an apparent cure by the addition of vitamin A (in cod liver oil) to the diet.



therefore represents largely a pseudohypertrophy.

**Vitamin B Deficiency (Beriberi, Pellagra).**—The vitamin B complex is now known to include at least two distinct nutritional factors. The first or heat labile factor ( $B_1$  or vitamin I) is the antineuritic or antiberiberi factor which will perhaps continue to be called vitamin B. The second or heat stable factor ( $B_2$ , P, P' vitamin I or G) is the more recently discovered growth promoting or antipellagra factor. In the earlier work these two factors were not distinguished so but little is yet known as the detailed effects of their individual deficiencies separately.

In human beriberi a variable amount of renal parenchymatous degeneration has been reported but usually no signs of nephritis. The passive venous congestion so frequently found in the kidney and other organs may perhaps be ascribed to the weakened heart muscle. I have found urinary calculi relatively frequent in malnourished Filipinos especially those with beriberi.

Renal disturbance (involving albuminuria, hematuria, etc.) in cases of human beriberi was noted also by Kepler, Moore, and



especially in young individuals, tends promptly to recover its normal weight and structure, unless the lesions are unusually severe. In some cases, however, the renal abnormalities may persist after the body in general has been restored to apparently good condition.

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## CHAPTER IX RENAL COUNTERBALANCE

By FRANK HINMAN M.D.

**Definition.**—There are two facts which form the basis of renal counterbalance. These are that the renal mass is divided into two equal portions, a right and left kidney, and that injury or disease usually is circumscribed and only rarely diffuse and uniform. Even when bilateral the majority of renal injuries are unilateral. By counterbalance is meant the anatomical and functional readjustment between the less injured or uninjured portion and the more injured portion in the performance of the total work required. A discussion of this readjustment requires the consideration of renal reserve in relation to the changes of hypertrophy and of atrophy.

### EXPERIMENTAL CONSIDERATION OF RENAL COUNTER-BALANCE

**1 Renal Reserve.** There has been some confusion as to what constitutes renal reserve and it is a popular conception that the remaining kidney if normal is able immediately to take over the extra burden occasioned by removal of its mate. Upon closer consideration this is found to be only partially true and renal reserve is seen to be largely potential and to have both an anatomical and a functional correlation. It is a fact that the renal reserve of different species of animals is not the same. Small animals have large kidneys and a great anatomical reserve. In large animals the anatomical reserve is small. In man, however, by a great many dissections it has been shown that the normal renal mass may be reduced to one-third or even one-fourth and the animal may survive. The remaining kidney substance constitutes the minimal amount of renal mass compatible with life and it is found that this one-third or one-quarter portion has undergone remarkable hypertrophic changes. The functional reserve on the other hand has been tested experimentally by a study of the function of the remaining healthy kidneys after unilateral nephrectomy. We have found that at first this kidney is unable completely to make good the loss of its mate so that during the first five or six days there is a relative

renal insufficiency. This initial insufficiency can be demonstrated also by the results following the ligation of one branch of the renal artery. These insufficiencies however, are not proportional to the amount of the renal mass thrown out of action and the insufficiency is removed very quickly by an anatomical hypertrophy of the renal mass remaining. Renal reserve thus is seen to be of two types: the native reserve which is the normal physiological response to stimulation such as is possessed by all glands and organs and an acquired reserve which is the repair by growth or compensatory hypertrophy in response to overstimulation.

2 **Renal Hypertrophy**—Consideration of the changes incidental to renal hypertrophy or repair requires a thorough understanding of the structure of the kidney. In addition it is at once necessary to distinguish between renal hypertrophy and renal hyperplasia

though only to a very slight degree up to the fifth or sixth year

take into consideration these two facts. In an adult animal's kidney it has been found by careful measurements that growth concerns particularly two structures of the kidney, namely the glomerulus and the proximal convoluted tubular area. It also has been estimated that from twenty to thirty days usually are required

repair is the result of hypertrophy. There are two groups distinguishable—in one the change is by a diffuse mass hypertrophy; in the other by a circumscribed or group hypertrophy.

An example of mass hypertrophy is the commonly observed unilateral growth of one kidney following removal or loss of its mate. Some interesting experiments have demonstrated that this mass type of hypertrophy may be bilateral. A typical bilateral mass hypertrophy has been produced by transplantation of one ureter into the duodenum, a procedure which throws out as far as actual excretion is concerned the work of one kidney, but because this kidney continues to receive the same blood supply it undergoes a compensatory hypertrophy hand in hand with that of its mate.

which actually does all of the renal work. As seen below, however, is circumscribed rather than diffuse, and is circumscribed rather than diffuse in a consideration of renal counterbalance. This type of growth may be tested experi-

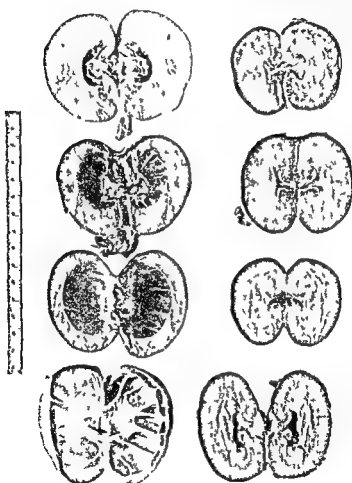


FIG. 24.—Closed hydroureter shows in dogs of an equal size of seven, fourteen, twenty-one, twenty-eight, thirty-five, forty-two, forty-nine, and fifty-six days duration. The opposite hydroureter is shown.

mentally by a comparison of the results of three types of repair following relief of ureteral obstruction in hydroureter.

The distribution in groups of the pathological changes of hydroureter gives a reasonable expectation that the less injured groups of glomerulotubular units may recover considerable func-

tional ability after removal of the obstruction. The easiest way to test this is simple. Doubly ligate and divide a ureter. The bladder is possible so that when the time comes to remove the obstruction in order to study repair the end freed of it can be implanted in the bladder. It is found (a) That the rabbit or dog cannot survive a complete ureteral obstruction of longer than two to three weeks if the opposite kidney is not at the time of the implantation. (b) that a hydronephrosis of four weeks duration may repair sufficiently to carry out function with survival of the animal if there is a delay of months between this implantation and removal of the obstruction. (c) that a hydronephrosis of thirty to forty days duration may undergo sufficient repair to perform the needs of the animal efficiently if the burden is shifted gradually after ureteral obstruction by a slow destruction of the compensatory kidney or by a partial obstruction of its ureter.

It is found also that functional compensation of the kidney occurs much more quickly than anatomical compensation which is not complete for from thirty to forty days. When an anatomical compensatory hypertrophy has occurred in the opposite kidney the changes of repair on the hydronephrotic kidney (necessarily a hydronephrosis of more than thirty to forty days duration of the ureter) are reduced to a minimum and repair is manifested may in time disappear. A hydronephrosis of sixty to ninety days duration will show repair nodules on removal of the obstruction but these are functionally inactive and will disappear unless given some unusual stimulation. It would follow a severe injury to the compensatory mate.\*

Repair of hydronephrotic atrophy following removal of obstruction

in size

of the

normal appearance. The glomerular and convoluted portions of these repaired groups will show hypertrophic changes. Recovery of function will be proportional not only to the number of structural units in which repair takes place but also to the degree of hypertrophy of each. With repair the same stage of hydronephrosis or destruction will show in different kidneys a variation in the nature of these hypertrophic changes according to the nature of the

tory burden placed on the kidney at the time the obstruction of the ureter is removed. The maximum repair of structure and restoration of function will follow a gradual shifting of the burden such as takes place after the slow destruction of the opposite kidney.

**3 Renal Atrophy.**—Renal atrophy has been regarded almost universally by pathologists as degenerative in type and caused by bacterial, chemical or other toxins, producing the well-recognized pathological condition of cloudy swelling and fatty, amyloid and



FIG. 25.—Left, unilateral compensatory hypertrophy. Right, ureter implanted in duodenum for four hundred and forty three days.

	Weight gm.	Length cm.	Width cm.	Depth cm.
Right	27	5.3	1.9	.85
Left	44	6.0	2.5	3.05

hyaline degeneration. There is also a well-recognized type of atrophy (which may be termed biological) which is caused by inanition, pressure or inactivity, and it is possible to produce experimentally what would seem to be a renal atrophy from disuse. For instance, the late atrophy following the early repair which takes place upon the relief of obstruction in hydronephrosis of thirty to forty days, when the opposite kidney has been undisturbed and has undergone compensatory hypertrophy during the period of unilateral block.

results from insufficient stimulation. Another example of atrophy from disuse is furnished by the experiment of ureteroduodenostomy mentioned above in which it was shown that if the animal were examined within sixty to ninety days after the transplantation there was a compensatory hypertrophy of the kidney whose ureter had been transplanted into the duodenum. On the other hand if the animal were allowed to survive for a period of two years or more this initial hypertrophy had disappeared completely and the kidney was found to be small almost functionless or completely atrophic. The explanation of this late atrophy following an early hypertrophy after ureteroduodenostomy is not altogether clear but it seems reasonable to assume that it results from a gradually diminishing stimulation or loss of work. In a successful experiment infection did not occur to produce atrophy, there was no back pressure or ureteral obstruction to cause it and it is doubtful if one might presuppose toxic injury from ascension of the contents of the duodenum into the pelvis of the kidney to cause it. Yet atrophy occurred. On the other hand it is a well known fact that the activity of the kidney is not continuous and there are periods of inhibition or lessened activity. In this experiment whenever the kidney whose ureter was transplanted into the duodenum took a rest period the accumulation of waste substances in the blood was not influenced because the opposite kidney was doing all the work of actual excretion. Such rest periods therefore do not lead to any subsequent hyperactivity. Any rest period of the compensatory kidney on the opposite side however must be paid for by an increase of activity later. This difference in burden of response with rest and the greater predisposition of the transplanted kidney to inhibition (and rest) would account for the gradual progressive and late atrophy an example therefore of the atrophy of disuse. (Figs 26 and 27.)

which respect to hypertrophy  
and equilibrium

which following

the complete obstruction of one ureter is so uniformly progressive in like animals of similar weight that for purposes of experiments on repair the same periods of obstruction may be assumed to produce essentially identical degrees of injury. (Fig 24.)

The compensatory hypertrophy of the opposite kidney is progressive and requires thirty to forty five days to become anatomically complete. It is probable that in this time the functional reserve power has not yet reached its maximum.

In early stages both the hydronephrotic atrophy and the compensatory hypertrophy show a markedly circumscribed distribution. Neither the injury nor the repair is diffuse or uniform.

After removal of the obstruction of the ureter, repair of the early stages of hydronephrosis occurs by restoration and hypertrophy of the less injured or uninjured groups of glomerulotubular units. Hydronephroses of less than two weeks' duration show a remarkable degree of repair, but in obstructions that have lasted longer than ninety days there is almost no repair.

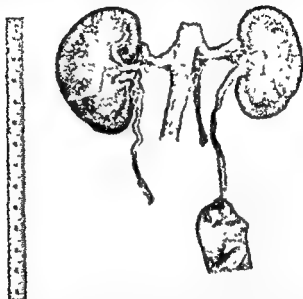


FIG. 28.—Right compensatory hypertrophy and left repair two hundred and forty nine days after ureterostomy for a closed hydronephrosis of twenty one days. Relative phenolsulphonphthalein before sacrifice of animal.

	4 min	8 min	
First appearance in			
First fifteen minutes	25	5.0	
Second fifteen minutes	20	3.3	
	—	—	
Total	45	7.5	
Kidney weight at necropsy	49 gm.	15 gm.	

No evidence of infection. Urine clear without pus or bacteria, and sections show no leukocytic infiltration. But glomeruli and tubules are small in comparison to those of right kidney. This kidney of twenty-one days' obstruction is just at the borderline between permanent repair and late atrophy. (Compare with Fig. 29.)

In cases of hydronephrosis of the same degree and duration, the repair which follows removal of the obstruction will vary in proportion to the functional need of repair. This need can be modified considerably by injury or removal of the opposite kidney.

If the opposite kidney is undisturbed, there will be no permanent



## RENAL COUNTERBALANCE

repair following the relief of obstructions of longer than forty-five days and but little after thirty days because the compensatory hypertrophy of the opposite kidney has removed the need for it. The early and rather insignificant repair of a hydronephrosis of thirty days' duration is rarely permanent. Opposite nephrectomy at the same time as the hydroureterocystostomy results fatally in most closed hydronephroses of more than fourteen days' duration, but if the nephrectomy is delayed a few weeks, many dogs with



FIG 27 —Roentgenogram after arterial barium sulphate injection showing vascular attenuation of the right kidney whose ureter had been transplanted into the duodenum for two hundred and forty-nine days (shown in Fig 26)

hydronephroses of twenty-one days' duration will survive. If an autonephrectomy is produced gradually by partial obstruction of the opposite ureter, a kidney in which a closed hydronephrosis has existed for thirty to forty days may so repair as to perform total function efficiently (Fig 28). The degree of repair of hydronephrosis after opposite nephrectomy, although the ultimate need for repair is the same, will vary according to whether nephrectomy is performed at the same time, after some delay, or gradually, with an optimum degree of repair in the last instance. The results of these experiments point to two factors of importance in the control of the growth of the remaining renal units after the loss or injury of others. One is reserve power sufficient

to permit hypertrophy and the other is stimulation of such type and degree as to promote it.

At present we are in no position to explain specifically what constitutes renal stimulation. Blood supply is not fully synonymous though the chemical composition of the blood no doubt plays a rôle. The phenomenon that the different portions of the kidney respond to renal stimulation with different degrees of hyper-



FIG. 4.—Removal of a thirty-one-day left clone by four days after partial nephrectomy of right ureter by stretching a rubber band also it is seven days after the left anteroposteriorotomy. On day of an eight total when is the nephrectomy first he is 31 per cent weight 1 hour .00 per cent. Urea nitrogen 1.0 mg per cent nitrogen 41 mg per cent. At necropsy (ether) the right kidney is a large hydronephrotic sac containing 40 ml of fluid with a small remnant of renal tissue at the lower pole. The left pelvis has a capacity of 5 cc. The microscopical shows hypertrophy of glomeruli and tubules without infection.

trophies (the proximal convoluted tubules enlarging 60 per cent the glomeruli 20 and remaining portions less than 10 per cent) is deserving of special consideration. I need feeding of urea over long periods does not cause this type of hypertrophy in the uremic blood stream. But the injection into normal dogs of the uremic blood from nephrectomized animals causes a bilateral hypertrophy in every respect analogous to the compensatory growth following unilateral nephrectomy and double nephrectomy in the other. Renal tumors causes hypertrophy of both kidneys in need of analysis stimulation and renal work are general terms in need of analysis based upon more detailed knowledge of renal physiology. Renal work can be relative only never complete. Activity is relative to intensity for groups of renal units as well as for the unit itself. Periods of rest and of work for each unit have been demonstrated by direct observation but the concept that whenever a unit works,

it works to full capacity is no longer tenable. Though tubular activity is correlated with glomerular work and a glomerulus with its tubular system forms the structural unit of the kidney the functional unit is larger with the blood supply as its basis and comprises a group of structural units with a common blood supply. A consideration of the details of the vascularization supports this view. All the blood reaching the tubules already has been depleted of certain substances while passing through the glomeruli but the blood passed to this loop

of one and the same unit might each receive independently blood from different glomeruli. Characteristic of the secondary capillary bed are its extensive anastomoses. In short each functional unit is a colony of interdependent individuals and the completed work of urine formation is accomplished by the group not the individual.

In harmony with these considerations is the occurrence of group atrophy and group hypertrophy and in all renal diseases with group distribution of the injury and of the repair the theory of counterbalance is applicable.

### CLINICAL CONSIDERATION OF RENAL COUNTERBALANCE

In the application of these experimental considerations the clinical problem is made difficult and uncertain because of our continued ignorance of the mechanism of renal activity, and because of the defects in the clinical estimation of this activity. All tests of function are purely empirical and they have the added defect of indicating renal work for the period of the test and for that period only. They give no indication of what the kidney has done or will do. They are also extremely uncertain guides as to anatomical conditions and because of the incidence of inhibition and hyperpermeability are frequently inaccurate.

In addition to function as indicated by these clinical tests the surgeon must estimate the anatomical condition of the kidney. This information is furnished by the technical methods of examination. Before operation a good idea of the condition of the healthy kidney and of the injured kidney is possible.

Renal counterbalance possibly is not of the same significance in the medical diseases of the kidneys as in the surgical. But islands of injury and of hypertrophy are found in most types of Bright's disease and the possibility of removing the injury and stimulating hypertrophy deserves consideration. The fact that the repair the excess of stimulation  
Investigation as

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kidney is capable of doing. Nevertheless, they are of great help when interpreted in the light of our clinical inference in regard to the pathological changes present. The application of the theory of renal counterbalance is an attempt on the part of the surgeon to predict the final adjustment of the renal mass which is left after any one of a number of surgical procedures. In many conditions, operative treatment is open to serious consideration. Sometimes nephrectomy is too radical a conservative procedure being to the best interest of the patient at other times removal of the diseased kidney is the part of good judgment. Prescience of the renal mass and of its reserve power and of the type and degree of stimulation it will receive establishes the basis for forecasting the final counterbalance after the proposed surgical interference. Irrespective of

on each side its relative activity, health and reserve power is possible by correlation of a number of clinical and urological facts: (1) the history, (2) the urine, (3) the total renal function, (4) the findings of ureteral catheterization as to infection and relative function, (5) the size of the kidney shadow in relation to the shape and size of its pelvis (pyelogram) which indicates the amount and thickness of renal parenchyma.

These studies aided by other more special ones when indicated give a good clinical estimation of the anatomical and functional condition of each kidney. The reserve power and the potentiality of repair may be tested in obstructive conditions by placing retention ureteral catheters for several days and determining if relief of obstruction gives improvement in function. If not possible satisfactorily to relieve obstruction by the use of a ureteral catheter preliminary nephrostomy (preferable to pyelostomy) for a few

obstructions, or unilateral ones when the other kidney has been removed previously. In a number of cases with only a faint trace of phenolsulphonephthalein excretion in two hours and marked

nitrogen retention (urea nitrogen 300 to 400 mg and creatinine 12 to 14 mg per 100 cc) nephrostomy under spinal anesthesia bilaterally when both kidneys were involved has restored function so that later ureterovesical implantation or other conservative surgery undertaken to relieve the obstruction permanently could be performed successfully. Sometimes the plastic repair may be done at the time of the nephrostomy thereby relieving the patient of a second operation. A girl with one tuberculous kidney removed the bladder contracted and useless and the other ureter involved and obstructed by the same lesion had a marked renal insufficiency as indicated at the time by no output of phenol sulphonephthalein and a high retention of nitrogen. A well functioning nephrostomy tube draining into a rubber urinal fastened to her leg has resulted in considerable renal repair and keeps her free from pain and bladder distress and has enabled her to live for more than three years in comparative comfort. Her total phenol sulphonephthalein excretion now averages 30 to 40 per cent.

These desperate cases and others like them are clinical proof of the remarkable potentiality of repair of renal tissue when the cause of injury is removed and the need of repair is urgent. Conservative surgery should be the rule for all bilateral lesions; nephrectomy the exception.

In unilateral abnormality repair of lesions anywhere near as advanced as the bilateral ones just mentioned is not to be expected. The factors of renal counterbalance explain the apparent discrepancy. The good kidney must be able to support total function.

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involvement of the good kidney is greater and the surgical treatment therefore should be more conservative. But it shows poor judgment to leave as a source of future trouble badly infected tissue that drains poorly or has pockets of urinary stasis and never would be able to support life alone under any circumstances.

The theory of renal counterbalance cannot be formulated into rules of guidance in these problems but knowledge of the theory and the factors involved will help in the proper correlation of the clinical and urological facts in surgical conditions.

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# PART I

## CLINICAL ASPECTS OF RENAL FUNCTION. —

### CHAPTER V

#### CERTAIN CHEMICAL ASPECTS OF RENAL FUNCTION

By JAMES I. GAMBLE, M.D.

**Introduction** The Requirement for Acid base Control — We properly regard the essential task of the kidney as consisting in a removal of water and substances from the blood plasma in terms of the requirement for closely stationary concentrations of the individual crystalloids in the blood plasma and in the body fluids behind it. In our studies of renal function our admiring curiosity is chiefly focussed on this maintenance of prescribed concentrations. Incidental to this control there is however an interesting stipulation, viz. that the reaction of the urine be held within certain bounds. This requirement derives from the circumstance that maintenance of plasma concentrations usually demands removal of plasma base and acid in widely unequal amounts. There is thus obvious need for defensive adjustments to prevent the production of urine at a devastating degree of acidity or alkalinity. This is accomplished by a regulatory mechanism which has been brought into view chiefly by the work of I. J. Henderson. The purpose of this chapter is to describe the factors of this control and by means of quantitative data display them in actual operation in various situations of acid base metabolism.

#### THE ACID-BASE COMPOSITION OF THE BLOOD PLASMA

The relative values of the basic and acid factors are here represented the former being superimposed in the left hand and the latter in the right hand column. It should be noted here that plasma acid must be covered entirely by fixed base the minute concentration of ammonia permitted being relatively negligible. This circumstance is an important premise in the regulation of acid-base excretion. It should also be mentioned that two of the factors shown in the diagram the concentrations of protein and of bicarbonate ion ( $\text{HCO}_3^-$ ) are not directly under renal control. The role

accomplished by the operation together of the two above-described

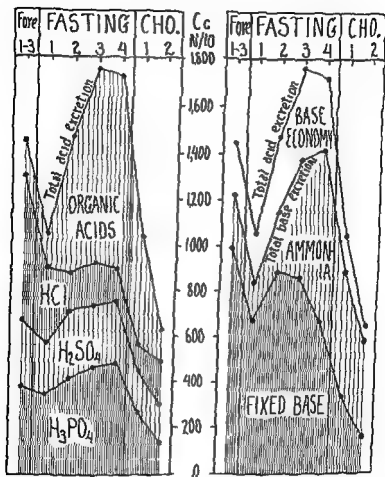


FIG. 30—Illustrating the excretion in urine of a varying excess of acid over fixed base (Gamble J Biol Chem)

illustrate this control. These measurements were obtained from consecutive twenty-four-hour urine specimens collected over a three-day foreperiod followed by four days of fasting and a two-day afterperiod during which the only food given was a small amount of carbohydrate in the form of cane sugar. The subject was an epileptic boy who was fasted as a therapeutic measure. The basic and

acids must be conveyed into the urine. The administration of a small amount of carbohydrate removes this ketosis and also by its protein-sparing effect reduces the quantity of other acid radicles and of fixed base presenting for excretion. The conditions of this experiment should therefore extensively exercise the control factors which guard the fixed base level in the plasma.

In the left-hand diagram the four urine acids are shown. Their values are recorded in terms of their base equivalence at the reaction of the blood plasma.\* The measurements of the individual acids are superimposed so that the uppermost line describes the total acid excretion. The large extension of the organic acid factor due to ketone acids produced during the period of fasting is evident.

acid values and thus produce a line showing the actual amount of base in the urine. Laying off downward again the values found for ammonia another line is established which describes the fixed-base excretion†. It is apparent from these diagrams that total acid which while being conveyed to the kidney must be completely covered by fixed base is permitted to carry only about one half of its equivalence of fixed base into the urine. The alertness of the control factors in the presence of a developing and dictated by the perignations excretion. As regards the ed that direct measurements of the concentration of fixed base in the blood plasma of this subject demonstrated an accurately sustained value.

## RESPONSE OF THE AMMONIA FACTOR IN NEPHRITIS

Discussion of the much debated but still unsettled question as to whether the locus of the regulated production of ammonia is in the kidney or elsewhere will not be undertaken. It may however be appropriate briefly to present data which indicate that disease of the kidney is accompanied by a slower than normal response of this factor following ingestion of acid producing salts. These data

\* That is the quantity (0.1 N HCl) found in the urine was multiplied by 1.2 to obtain its base equivalence at the reaction of the blood plasma, and the full value of the base content of the organic acids was used. The base equivalence of hydrochloric acid and of sulphuric acid is of course the same in urine as in the plasma.

† By way of verification of the principle on which the construction of these diagrams is based direct measurements of the fixed base excretion were made and were found to agree closely with the values found by subtracting Total Acidity + Ammonia from Total Acid.



## 170 CERTAIN CHEMICAL ASPECTS OF RENAL FUNCTION

are given in Fig. 31. They consist in measurements of the increase

noted that the ingested ammonia is not conveyed through the body fluids but is directly after absorption converted into urea so that

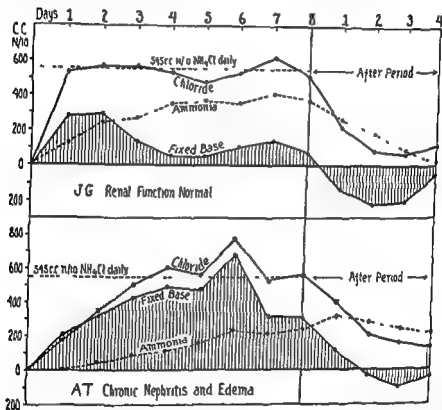


FIG. 31. Showing slower response of ammonia factor in the presence of an increase of acid excretion in a patient with nephrosis and edema (lower diagram) as compared with the values found for a normal subject (upper diagram) (Gamble J Clin Invest courtesy of Williams & Wilkins Company)

the ammonia used to cover the excretion of chloride ion must be obtained from urea just as would be the case if the chloride ion were provided by ingestion of hydrochloric acid instead of ammonium chloride. The upper diagram describes the findings following ingestion of ammonium chloride by a subject with normal kidneys. There is evidently an appreciable lag in extension of the ammonia factor permitting withdrawal of fixed base. After 2 days or two the ammonia increase fairly closely covers the chloride excess and

after the ingestion period it remains elevated and thus permits the loss of fixed base to be rapidly regained. The measurements from which the lower diagram is constructed were obtained from a patient with nephrosis who was edematous. Here the rise in ammonia production is slow and permits a large withdrawal of fixed base which is only to a slight extent regained in the after-period. This loss of fixed base was accompanied by removal of the patient's edema—a presumably desirable event so that there is here opportunity for debate as to whether the slow response of the ammonia factor represents an adjustment suitable to the circumstances or whether the diuresis should be regarded as obtained by taking advantage of a disabled ammonia mechanism.\*

### MECHANISM OF THE EXCRETION OF EXCESS FIXED BASE

Having illustrated the operation of the regulatory factors which convey an excess of acid over fixed base into the urine, control of the much less usual reverse situation produced by an excess of fixed base over acid presenting for excretion may now be considered. Obviously the requirement here is for an acid analog of ammonia that is for an acid substance abundantly at hand which can be controllably placed in the urine. Carbonic acid suits these specifications ideally. Its availability is practically unlimited. Routinely it leaves the body base-free by way of the lungs but when needed can to a regulated extent be deflected into the urine.

A study of the carbonic acid and bicarbonate values found in a sample mechanism

The concentration

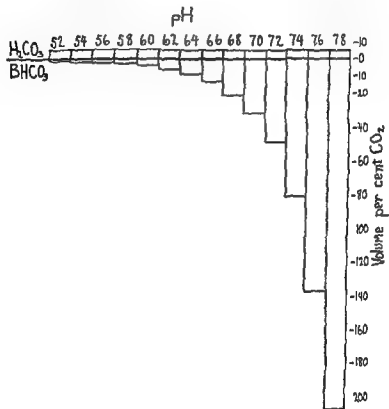
inary value and is

moreover of approximately the magnitude which obtains in the blood plasma. In other words, the carbonic acid concentration differs strikingly from the concentrations of all of the other substances in urine by remaining in balance with the blood plasma level. As a consequence of the fixed value for carbonic acid the concentration of bicarbonate in urine becomes a direct function of

\* In this factor

† For the hydrogen ion concentration of a solution containing free carbonic acid and bicarbonate is determined by the ratio of the concentrations of the two substances; if one factor remains stationary the other must vary directly with pH. Therefore the constant value for free carbonic acid produces a fixed value for bicarbonate for each degree of hydrogen ion concentration.

of the blood plasma (7.4) the concentrations of bicarbonate become rapidly enormous. Evidently we have here the mechanism which establishes the alkaline bound of urinary reaction. The concentration of bicarbonate which in the presence of the immovable level of carbonic acid would be necessary to force the pH of urine above 8 approaches the limit for the total concentration of sub-



stances in  
amounts of  
above pH 6

Another diagram is the relatively small quantity of bicarbonate in urine in usual reaction. Compare for instance the concentration of bicarbonate at pH 6 with that found in urine of the reaction of blood plasma

and that reaction of large alkalinity

# MECHANISM OF EXCRETION OF EXCESS FIXED BASE 173

**pH 7.4** Avoidance of a useless expenditure of base as bicarbonate can, therefore, be recognized as a chief significance of the usual reaction of urine. Inasmuch as carbonic acid may leave the body base free by way of the lungs base entering the urine as bicarbonate.

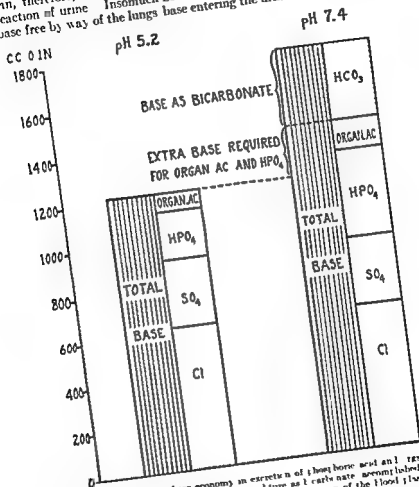


FIG. 31 Illustrating base economy in excretion of phosphoric acid and organic acids and also the prevention of base expenditure as bicarbonate accomplished by the production of urine at pH 5.2 instead of at the reaction of the blood plasma pH 7.4

is obviously completely wasted and such an event in the presence of the usual circumstances of acid base metabolism which demand a conservation of base would be a physiological solicism. The saving of base gained by the excretion of acid instead of alkaline phosphate and of uncombined organic acids has been considered

above. This adjustment produces an acid urine and thus incidentally accomplishes an additional service to base conservation by almost completely preventing a large wastage of base as bicarbonate. Actually the base thus indirectly conserved is a larger quantity than the economy of base obtained in the excretion of phosphoric acid and the organic acids. This point is illustrated by the diagrams in Fig. 33 which are constructed from measurements of the four urinary acids obtained from a twenty-four hour collection of urine. The left hand diagram describes their total base equivalence at pH 5.2 which was the actual reaction of the specimen. The right hand diagram shows the quantity of base which the specimen would contain if produced at the reaction of the blood plasma pH 7.4. The extension of the base equivalence of  $\text{HPO}_4$  and of the organic acids at this pH is indicated and also the additional and larger quantity of base which would be present as bicarbonate.

Although an ordinary dietary regime produces the requirement for a more rapid removal of acid radicals than of fixed base from the plasma, the reverse situation demanding defense of plasma acid (especially of its salient factor chloride ion) occasionally arises. From the above discussion of the pH bicarbonate relationship in urine, the mechanism at hand is apparent. As may be seen by glancing at the diagram in Fig. 32, slight increments of urinary pH will rapidly accommodate for the removal of base as bicarbonate and relatively huge amounts can be removed within the alkaline bound of urine. A diet composed of vegetables and fruits will moderately exercise this mechanism. In the case of the herbivora it is of course steadily in operation. The data which are here presented by way of quantitative illustration were experimentally obtained but are descriptive of the situation produced clinically by the treatment of the state of dehydration caused by upper intestinal obstruction. The measurements recorded in the diagrams in Fig. 34 are from consecutive twelve hour urine specimens obtained by catheter from a female dog following an experimental obstruction of the pylorus. The dog was given as indicated on the diagram large intraperitoneal injections of physiological sodium chloride solution. Following obstruction there occurs an extensive withdrawal of body fluid caused by the continued loss of gastric secretions. There is also the feature that a deficit of chloride ion is produced which is much larger than the accompanying deficit of fixed base (sodium) owing to the relatively much greater quantity of the former in gastric secretions. Consequently when sodium chloride solution is given abundantly the deficit of sodium will be repaired long before the loss of chloride ion is replaced and the kidney will then be called upon to remove sodium and retain chloride ion. In the left hand diagram of Fig. 34 the measurements of the

acid factors are superimposed and in the right hand diagram those of ammonia and of fixed base are recorded. It may be seen that throughout the experiment the chloride-ion content of the urine

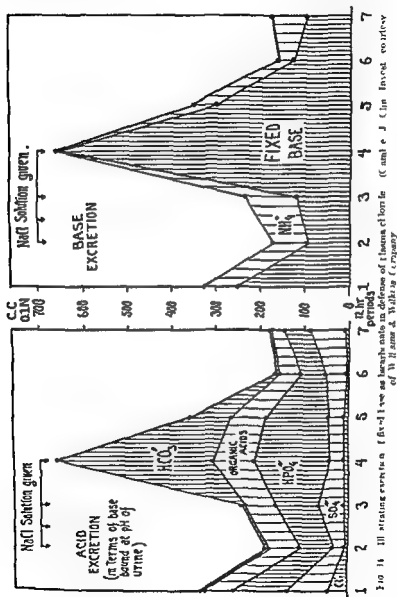
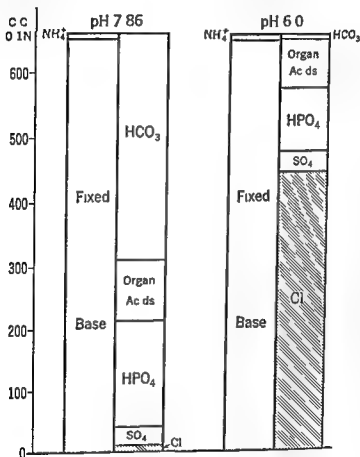


FIG. 16. III. Urinating even from 1 fix-1 live as lucubrations in defense of plasma chloride (C. and J. Clin. Invest. 1934) of W. H. and A. Walker (C. and J. Clin. Invest. 1934)

remains minute whereas after the first two injections of salt solution the fixed base excretion rises extensively and in the diagram of acid factors is accompanied by a covering rise of bicarbonate ion

The reaction of specimen No 6 which contained most of the bicarbonate was pH 7.8. It is incidentally interesting although



... that the

plished by the excretion of sodium bicarbonate the actual position of specimen No 6 is given in the left hand diagram of

Fig. 35, and in the right hand diagram is shown what would have been the composition of this specimen if produced at a usual urinary reaction pH 6.

We thus find that the composition of the blood plasma is admirably defended against the assault of either acid or alkali by mechanisms which are widely extensible and which are capable of operating within the bounds set for the reaction of urine. The parts of this defensive machinery are clearly in view. They can be seen to adjust themselves with a beautiful alertness and accuracy to rapidly varying situations. The secrets however of their motivation and self regulation fortunately remain to be learned.

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## CHAPTER XI

### THE OPTIMAL WATER REQUIREMENT IN RENAL FUNCTION

By JAMES L. GAMBLE, M.D.

**Introduction**—The experiments which will here be briefly described represent a very simply devised attempt to learn in approximate terms the quantity of water which best suits the conveyance and excretion in urine of urea and of several salts. Progressive increments of these were fed to rats and the corresponding extension of water intake observed. Levels of ingestion were reached at which the substances added to the basal diet constituted 90 per cent or more of the total quantity of materials claiming excretion in urine. Measurements of the water intake produced by these substances when fed singly or in mixtures may, therefore, be dependably compared. A feature of the observations is that they are long-conditioned, each measurement being obtained by an experimental period of one week.

#### THE WATER REQUIREMENT FOR SODIUM CHLORIDE AND UREA

The results of a sodium chloride and of a urea experiment are presented in Fig. 36\*. The diagrams in the lower part of the figure describe the method of providing the intake of these materials.

The composition of the basal diet is shown in the first column. The essential point is that protein and salt mixture were provided in amounts minimal for satisfactory nutrition in order to keep as low as possible the quantity of materials presenting for excretion in urine besides the added substance. Each of the steps in the addition of sodium chloride or of urea represents 1 millimol per gram of food. *In the case of the salt the millimol is an "osmolar one, that is, each increment was 0.5 millimol of molecular sodium chloride on the assumption of its practically complete ionization in urine.* In order to provide the diets with the same caloric value fat was increased and starch decreased appropriately for each dilution of energy caused by addition of salt or urea. The rats used in all of the experiments were nearly grown males of the same age.

\* The figures used in this chapter are reprinted with permission from the *Am. J. Physiol.*

and closely of the same weight. The data from each experiment were produced by feeding the animals a diet containing a certain amount of sodium chloride and a drink

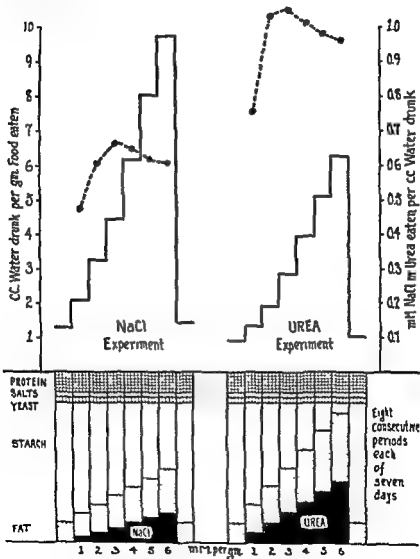


FIG. 36

# 180 OPTIMAL WATER REQUIREMENT IN RENAL FUNCTION

ments of food eaten and of water drunk were made daily. The individual periods of an experiment were each of a week's duration.

basal measurement. The points connected by the broken lines represent the concentration of ingested sodium chloride or urea in

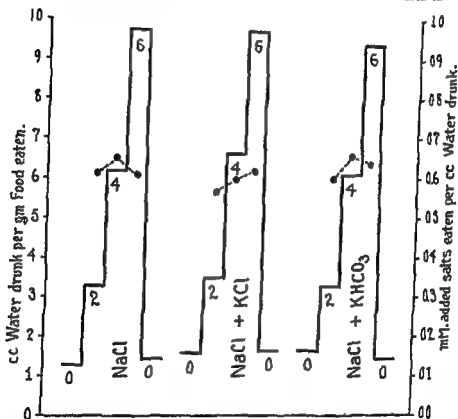


FIG 37

terms of the accompanying water intake. In both experiments, when the food contains 2 or more millimols of added substance per gram, these values are established at fairly stationary levels that for sodium chloride being approximately 0.6 M (osmolar), whereas for urea a much higher value, approximately 1 M is found. It is quite clearly the evidence of these data that the optimal water requirement for the conveyance and removal in urine of ingested sodium chloride is much larger than for equivalent amounts of urea.

### THE WATER REQUIREMENT FOR MIXTURES OF SALTS

The diagrams in Fig. 37 present for comparison with the data found for sodium chloride those obtained by adding to the diet mixtures of equal parts of sodium chloride and potassium chloride and of sodium chloride and potassium bicarbonate. In these experiments the food contained per gram 2.4 and 6 millimols of added materials in the three successive periods. As may be seen in the diagrams the levels of water-drinking produced by the salt mixtures and all of the concentration values in terms of the water intake agree closely with those of the sodium chloride experiment. It is therefore evident that the optimal water requirement produced by these several salts is identical or nearly so. Since this finding was obtained by using mixtures of the salts the additional information that the individual requirements are additive is gained.

### THE WATER REQUIREMENT FOR MIXTURES OF UREA AND SALTS

As has been noted (Fig. 36) the optimal water requirement for urea is less than obtains for these salts. This fact did not disturb an expectation that the requirements for salts and for urea would be found to be additive. The results of two experiments undertaken to test this point are presented by means of the diagrams in Fig. 38. The first column represents the water intake per gram of food when it contains 2 millimols of potassium chloride per gram. The next column measures the water intake in a diet containing 2 millimols of urea per gram. The water intake in a diet containing 4 millimols of added material composed of 2 millimols of potassium chloride and 2 millimols of urea is shown by the third column. The expected height of this column on the assumption that the individual water requirements are additive is shown by the broken line and the expected concentration of the mixture of ingested substances referred to water intake is indicated by a circle. The actual height is interestingly approximately double that of the urea column; that is it has the value which would be expected if the added 4 millimols of material were entirely urea and in consequence the concentration value found for the mixture of potassium chloride and urea referred to water intake is about the same as for urea alone. Repeating the experiment using larger quantities of the substances gave as may be seen in the second section of the figure identical results.

**Conclusions.** The results of these simple experiments with rats consisting in measurements of the voluntary water intake accompanying increments of materials placed in a basal diet demonstrate (1) that the optimal water requirement for removal in urine of each of several salts studied ( $\text{NaCl}$ ,  $\text{KCl}$  and  $\text{KHCO}_3$ )

■ identical or nearly so and that the individual requirements are, at least closely, additive, (2) that the quantity of water required for removal of urea ■ much less than for corresponding osmolar amounts of the salts, (3) that the differing requirements for urea and the salts are not additive, the requirement for a mixture of equal amounts of urea and salt being approximately the same as for an equivalent quantity of urea alone

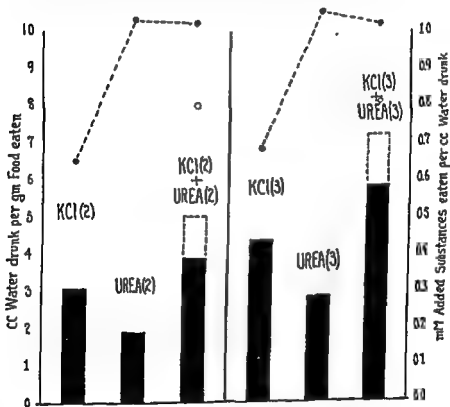


FIG. 38

The significance of the sum of these findings may be described as indicating an economy of water in renal function referable to urea \*

\* The sum of these findings may be described as indicating an economy of water in renal function referable to urea \*  
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1929 The optimal water drinking by in the food, Am J

## CHAPTER XII

### THE NON-EXCRETORY FUNCTIONS OF THE KIDNEY

By ISIDORE NAPPER M.D.

AND

MIRIAM GREENBAUM CURRIE

#### CONJUGATION BY THE KIDNEY

THE excretory function of the kidney is usually considered as its only function. It must indeed be its main one because nearly all urinary substances are also found in the blood without being formed in the kidney. Such is the case with urea, uric acid, sodium chloride, almost surely with creatinine and many other urinary constituents.

One instance of a different category of processes has been known for more than half a century. In a classical perfusion experiment on the excised kidney of a dog, Bunge and Schmiedeberg<sup>1</sup> showed that chemical synthesis takes place in the kidney: benzoic acid ( $\text{C}_6\text{H}_5\text{COOH}$ ) and glycine added to the perfusion blood were linked in the kidney to form hippuric acid, which was recovered from the perfusion fluid after one to two hours had elapsed. Detailed studies of this synthetic function formed the starting point from which followed the discovery of the oxidative functions of the kidney.

The importance of their discovery was increased when Bunge and Schmiedeberg showed that, as far as the dog is concerned, the synthesis of the hippuric acid takes place in the kidney only. If sodium benzoate and glycine were injected in the circulation of nephrectomized dogs, no hippuric acid could be demonstrated in the blood or organs of these dogs. Some years ago Kingbury and Bell<sup>2</sup> challenged these results. They did not deny that the kidney was able to perform the synthesis of hippuric acid, but they maintained that after injection of sodium benzoate and glycine in nephrectomized dogs hippuric acid could be detected in the blood and in the liver. It is of vital importance for this question to point out that Kingbury and Bell did not demonstrate the presence of hippuric acid; they showed the presence of benzoic acid conjugated with other substances, but did not prove that hippuric acid was formed. The authors<sup>3</sup> have several times repeated Bunge and Schmiedeberg's experiment and have not been able to find hippuric acid in the blood after injection of sodium

benzoate and glycine in the circulation of bilaterally nephrectomized dogs. The classical experiment of Bunge and Schmiedeberg still prevails: in the dog the kidney is the only organ which is able to form hippuric acid.

As pointed out by Bunge and Schmiedeberg there are other animal species for instance the frog and the rabbit where the kidney is unable to synthesize hippuric acid. In these animals it is probably the liver which has the power to bring about this synthesis.

It had never been proved that the human kidney is able to form hippuric acid. Using kidneys obtained by operation the authors were able to demonstrate that the human kidney is capable of this synthesis. Before the operation the function of (tumor) the kidney to be removed was shown by cystoscopic examination to be only slightly damaged. Immediately after operation the perfusion took place. Human blood to which sodium benzoate and glycine

synthetic and not merely excretory functions

had been  
 uric acid  
 excretion is disturbed. Investigating this problem<sup>22, 24</sup> we found a parallelism between the ab-  
 containing substances and it  
 remained an open question  
 sodium benzoate does not bring about the normal increase in the excretion of hippuric acid whether the low excretion is due to diminished synthesis or to retention. The authors were able to demonstrate that in cases where excretion of hippuric acid is almost completely inhibited synthesis takes place all the same. To patients in uremia with impaired hippuric acid excretion 15 gm

hippuric acid along with other nitrogenous waste products formed but is not excreted. Thus the hippuric acid tests in kidney diseases run parallel with and are to be considered in the same category as other nitrogen excretion tests.

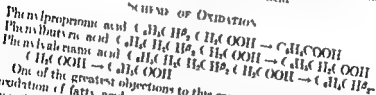
After ingestion of the homologs of benzoic acid characteristic conjugation products appear in the urine. When phenylacetic acid ( $C_6H_5CH_2COOH$ ) the first homologon of benzoic acid ( $C_6H_5$

(COOH) is ingested or subcutaneously administered the corresponding glycine compound, phenaceturic acid, is formed and excreted. Perfusion experiments with isolated mammalian kidneys showed that this synthesis can be accomplished by the kidney, considerable quantities of phenaceturic acid were recovered from the perfusion blood.

### OXIDATION BY THE KIDNEY

The fate of the higher homologs of benzoic acid the aromatic fatty acids is of importance primarily for our knowledge of fat metabolism since the complete oxidation of the aliphatic fatty acids to  $\text{CO}_2$  and water made difficult any insight into the mechanism at play. I put the isolation of the oxidation products of the aromatic acids rests our knowledge of fat metabolism. Knoop<sup>12</sup> demonstrated that any higher homolog of benzoic acid possessing an odd number of carbons in the chain is oxidized to benzoic acid (which may be considered as phenylformic acid ( $\text{C}_6\text{H}_5\text{COOH}$ ) and is excreted as hippuric acid and any homolog with an even number of carbons in the chain is oxidized to phenylacetic acid and excreted linked with glycine as phenaceturic acid.

### SCHEME OF OXIDATION



One of the greatest objections to this conception was the fact that oxidation of fatty acids *in vitro* never had been observed to occur via  $\beta$ -oxidation. Dakin<sup>13</sup> however has proved that by gentle oxidation of fatty acids with hydrogen peroxide the products of  $\beta$ -oxidation can be isolated *in vitro*.

Shortly after Knoop's publications bedside experiments of Sasha and Schwarz<sup>14</sup> with diabetic patients showed that  $\beta$ -oxidation of normal fatty acids increases ketosis.

Finally, Lindner<sup>15</sup> and his school proved by direct perfusion of the liver with blood to which fatty acids were added that the chains of aliphatic acids with an even number of carbon atoms are shortened in the liver by  $\beta$ -oxidation to butyric acid, which is partially oxidized yielding  $\beta$ -hydroxybutyric acid as a result of the perfusion experiments. It had not yet been possible to prove any corresponding oxidation of the aromatic acids by the liver though the  $\beta$ -oxidation of the aromatic acids by the intact organism was amply demonstrated by Knoop.

In perfusion experiments on the isolated mammalian kidney the authors obtained results analogous to those of Knoop. Perfu-



sion of the kidney of sheep and calves with glycine and phenyl

of the kidney was demonstrated

In later (unpublished) experiments it was found that the kidneys of Carnivora (dog) are not identical with those of Herbivora (sheep and calves) in their oxidative capacity. The authors demonstrated that the kidney of the dog oxidizes phenylpropionic acid ( $C_6H_5CH_2CH_2COOH$ ) only to cinnamic acid ( $C_6H_5CH=CHCOOH$ ) if one perfuses the kidney of a dog with blood to which phenylpropionic acid and glycine have been added the urine excreted during the experiment contains consider

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Phenyl  $\beta$  hydroxypropionic acid ( $C_6H_5CH(OH)CH_2COOH$ ) is hardly attacked by the isolated kidney of the dog only minute amounts of cinnamoylglycine are formed

It has been pointed out by Dakin<sup>2</sup> and especially by Quick<sup>17</sup> that cinnamic acid may be the first stage in the  $\beta$ -oxidation of phenylpropionic to benzoic acid. If this is the case then the kidney of the dog is able to bring about this first step and the complete oxidation of phenylpropionic acid to benzoic acid must take place in another organ. In confirmation the authors proved that the isolated liver of a dog can form benzoic acid if the organ is perfused with blood to which phenylpropionic acid or cinnamic acid or phenyl  $\beta$  hydroxypropionic acid is added

The oxidation of phenylpropionic acid in the  $\beta$   $CH_2$  group to benzoic acid in the kidneys of the calves and sheep may also take

scheme for the  $\beta$ -oxidation of phenylpropionic acid in the kidney of different species

Kidney of dog  $C_6H_5CH_2CH_2COOH \rightarrow C_6H_5CH=CHCOOH$

Kidney of calf  $C_6H_5CH_2CH_2COOH \rightarrow C_6H_5CH=CHCOOH \rightarrow C_6H_5COOH$

It is important to remember that the kidney is not the only organ in which  $\beta$ -oxidation occurs. The liver too is certainly capable of performing  $\beta$ -oxidation and as a result of this process large amounts of  $\beta$  hydroxybutyric acid are formed. The explanation is that through this type of oxidation butyric acid is formed from the naturally occurring fatty acids with their long chains of carbon atoms in even numbers and by the action of the liver butyric acid is partially oxidized to  $\beta$  hydroxybutyric acid. (Fatty acids with carbon chains of uneven numbers give rise to propionic acid and propionic acid perfused through the liver disappears completely.) Still under normal conditions the  $\beta$  hydroxybutyric acid content of the blood is insignificant and in normal urine  $\beta$  hydroxybutyric acid or other ketone body can scarcely be detected. So we must conclude that in the normal organism considerable quantities of  $\beta$  hydroxybutyric acid formed by the liver must disappear.

In current literature one always reads that the liver (see Wakeman and Dakin<sup>2</sup> and Marnett<sup>15</sup>) is able to oxidize  $\beta$  hydroxybutyric acid. This is correct only to a certain extent because during this oxidation only aceto-acetic acid and acetone are formed both products which like their mother substance are never found in normal body fluids. This partial oxidation of  $\beta$  hydroxybutyric must not be confused with the process by which the animal body gets rid of the large quantities which must be formed during fat metabolism. Partial oxidation similar to that occurring in the presence of liver cells has been shown to be reversible in the presence of normal tissue (von Lagermark<sup>24</sup>).

The solution of the question was difficult because of the inadequacy of our methods of determining traces of  $\beta$  hydroxybutyric in tissues. The technique of Engfeldt and Van Slyke can hardly be used for this purpose because of the interference of lactic acid and other substances. The authors have devised a method<sup>5</sup> suitable for this purpose and have been able to determine the fate of  $\beta$  hydroxybutyric acid in the liver.

They found<sup>26</sup> that during the perfusion of liver with blood to which  $\beta$  hydroxybutyric acid was added this substance was not converted to  $\text{CO}_2$  and water. We confirmed the work of other workers that during perfusion it is oxidized to acetoacetic acid. Calculations show that the entire amount which has disappeared is transformed into aceto-acetic acid. It is important to take into account the quantity absorbed by the liver cells during the trans-

further oxidized during perfusion through the liver. Some is reduced to  $\beta$ -hydroxybutyric acid and some is absorbed by the

sion of the kidney of sheep and calves with glycine and phenylpropionic acid, as was demonstrated

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 $\sim CH$

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further oxidized during perfusion through the liver. Some is reduced to  $\beta$  hydroxybutyric acid and some is absorbed by the

liver tissue. Therefore, the great quantities of  $\beta$  hydroxybutyric acid which must be formed during metabolism cannot be split up by the liver.

In view of the enormous oxidative capacity of the kidney which the authors had found in their previous experiments in which they showed that this organ is able to oxidize the resistant phenylbutyric acid to phenylacetic acid it seemed more than probable it is able to bring about oxidation of  $\beta$ -hydroxybutyric acid to smaller complexes and eventually to  $\text{CO}_2$  and water. During perfusion of the kidney with blood to which  $\beta$ -hydroxybutyric acid was added, not the slightest trace of aceto-acetic acid could be detected, though the greatest part of the  $\beta$  hydroxybutyric acid had disappeared.<sup>21</sup> Similarly aceto-acetic acid re-fore, we have to consider it to destroy the great quantities of acetic acid. It is well known that the normal metabolism

Are the  
Evidently

oxidizing ketone bodies

Summarizing one must conclude that the ketone bodies are formed in the liver and are oxidized in the muscles and kidneys

### **THE RÔLE OF THE KIDNEY IN CERTAIN INSTANCES OF DIABETES MELLITUS**

How is this oxidative power of the kidney and the muscles influenced by diabetes? Everyone knows that in diabetes mellitus the accumulation of  $\beta$  hydroxybutyric and acetoacetic acid in the body fluids is one of the greatest dangers which threatens the diabetic patient. What is the mechanism by which these ketone

has become a volcano which spreads great quantities of ketone bodies would kill by coma if there were no kidney and muscles

To determine whether the muscles of dogs suffering from phlorhizin diabetes and severe acidosis retain undiminished capacity of oxidizing ketone bodies the authors perfused<sup>36</sup> the kidneys and hind limbs of such animals adding  $\beta$  hydroxybutyric acid to the perfusion fluid. As the result of their experiments it appears that the kidneys and the muscles of the acidotic animals oxidize considerable quantities of ketone bodies. Thus they concluded that the oxidative functions of the kidneys are not primarily disturbed as an integral part of the diabetic alteration of metabolism.

What then is the relation of the kidney to diabetic coma? The acidosis of phlorhizin diabetes is evidently caused by the overproduction of ketone bodies by the fatty degenerated liver while kidneys and muscles are working hard to oxidize the enormous quantities of ketone bodies. A certain part of these hyperproduced substances cannot be oxidized even by the maximal function of kidney and muscles these are the circulating ketone bodies which cause the acidosis of the phlorhizin diabetic dog.

The condition of the diabetic patient then is partially dependent on the condition of his kidneys. As long as the latter are functioning normally as is the case in acute phlorhizin diabetes and most instances of diabetes mellitus the acidosis is kept within reasonable limits. When the catastrophe of diabetes occurs beginning with a complete breakdown of the glucose tolerance and a greatly increased production of ketone bodies and ending in coma there are at the beginning at least three different mechanisms at play by which the kidney combats the acidosis viz excretion of ketone bodies, oxidation of ketone bodies and increased ammonia production. In certain cases of severe diabetes mellitus which cannot be saved by insulin these functions break down and degeneration of the kidney is not infrequently observed. The following signs of damaged kidneys are known to occur in coma<sup>19, 20</sup> (a) Decreased

numbers (d) albuminuria when independently present varying with the degree of acidosis and (e) (Van Paasen<sup>37</sup>) impaired power of ammonia formation during and after coma.

That the various functions of the kidney are not independent but produce an additive strain on the kidney may be argued from the reaction of the kidney to Petren's diet. This diet in which such large amounts of fats are given can be endured only if the amount of protein administered at the same time is maximally restricted. The withdrawal of nitrogen-containing foodstuffs apparently eases the burden on the kidney thereby increasing its oxidative power so that it is able to cope with the hyperproduction

of ketone bodies arising from Petren's diet. As a matter of fact as soon as proteins are added to Petren's diet coma may be imminent.

Evidently then the renal insufficiency in diabetes must be a special one because oxidative as well as excretory functions are impaired. It must not be identified with the renal insufficiency of glomerulonephritis where only damage of excretory functions can be demonstrated.

In the majority of cases where the kidneys are healthy coma appears only if the quantities of  $\beta$ -hydroxybutyric acid (formed especially after an unreasonable diet) are so enormous that even the normal kidneys and muscles cannot handle this hyperproduction. These coma cases are cured by insulin. In two groups of patients in diabetic coma the administration of insulin does not bring about recovery. One consists of older individuals with arteriosclerotic changes the other consists of individuals in whom the acid

kidneys may play a role in the outcome.

Much interest has been given to the kidney lesions in diabetic coma. Some writers (Van Paasen<sup>13</sup> Metzger<sup>16</sup>) have found only small and insignificant lesions in the coma kidney. Others have described (Warburg<sup>14</sup> Ehrmann<sup>15</sup>) (a) Hyaline degeneration of the descending part of Henle's loop (Arminum) (b) glycogen degeneration (Ehrlich) (c) coagulation necrosis of tubuli contorti (Weigert) and (d) fatty degeneration of epithelia of the tubules.

**Summary**—1 The oldest known non-excretory function of the kidney i.e. the formation of hippuric acid is also performed by human kidneys.

2 Formation of phenaceturic acid i.e. the binding of phenyl acetic acid with glycocholic acid also takes place in the kidney.

3  $\beta$ -oxidation of phenylpropionic acid to benzoic acid  $\beta$  oxidation of phenylbutyric acid to phenylacetic acid  $\beta$ -oxidation of phenylvalerianic acid to benzoic acid are easily performed by the isolated kidney of the calf and the sheep.

4 Considerable quantities of  $\beta$  hydroxybutyric acid and acetoacetic acid are destroyed by the isolated kidney.

5 Also the muscles but not the liver are able to destroy ketone bodies.

6 In acute ketosis (phlorhizin diabetes) kidney and muscles have still retained the power of destruction of ketone bodies.

7 It is not improbable that in some cases of human diabetes impaired destruction of ketone bodies in the kidney may be one of the causes of ketosis.

8 The  $\beta$ -oxidation of the aromatic fatty acids is different in the kidney of different animals.





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## CHAPTER XIII

### THE PHENOLSULPHONPHTHALEIN AND OTHER TESTS OF RENAL FUNCTION

By LEONARD G. ROWNTREE, Sc D., M D

**Introduction.**—The history of the phenolsulphonphthalein test is of interest because it is the story of our first success in the investigation of the function of the kidney in disease. This procedure which has stood the test of time, was responsible for the conversion of the medical profession to a new idea. It demonstrated both the importance and the practicability of determining the functional capacity of the kidney in disease.

A tale of more than ordinary interest is told of Ira Remsen, formerly president of the Johns Hopkins University, who in his youth sponsored the birth of phenolsulphonphthalein. Toward the close of his life, a surgeon called on him under conditions

inquired as to the nature and purpose of this test. He was informed that the findings would determine whether or not he would have the operation. On further inquiry, he learned that it was the phenolsulphonphthalein test. It was a substance which he had known in his youth was being used in his old

Until 1900, renal function tests played but an unimportant rôle in the surgical examination of the patient and practically no rôle in the medical examination. Desultory studies had been carried on from time to time in some of the larger clinics, especially abroad, but the subject had not attained true clinical importance. The prevailing viewpoint of that period may be grasped from a leading medical authority who in the year 1910 says: "So far as our power of determining the functioning capacity of the two kidneys is concerned, I think we must rely upon an examination of the urine by means of the older and simpler methods, i. e., examination for

diverse. The results, of course, are not always reliable. They can,

perhaps in questionable cases be made more accurate by using the phlorizin test

The author's interest in the phthaleins was created by Prof John J Abel. In 1908 the author had the privilege of collaborating with him in a study of the pharmacological action of some of the phthaleins and their derivatives with reference to their behavior as purgatives the phthaleins being supplied by Remsen and by Orndorff. Our problem was to find a good subcutaneous purgative. Our most important findings however were (1) The low toxicity of various phthaleins (2) their laxative action particularly of the tetrachlor derivatives and their excretion through the bile and (3) the rapid elimination of the phenolsulphonephthalein by the kidney.

An effort was therefore made to determine whether phenol sulphonephthalein was better adapted as a functional test for the kidney than other substances already tried. This involved the application of the test to clinical cases and thus Dr Geraghty came into the study. He was a surgeon of outstanding ability a keen observer and indefatigable investigator and as true a friend and as fine a collaborator as ever a man could wish. Association with him was not alone a pleasure but from the standpoint of our work a matter of extreme good fortune. Scientifically we were supported by Dr Abel and clinically by Dr Hugh Young and Dr George Walker. Under these happy auspices Dr Geraghty and the author launched the phthalein test.

## EARLY STUDIES OF DISTURBED FUNCTION IN RENAL DISEASE

The earliest observations on the elimination by the kidney in disease were those of Hahn who noted the absence of the odor of violets in the urine of gouty subjects after the injection of turpentine and of Rayer who noted the absence in nephritis of that peculiar odor which normally is present in the urine after eating asparagus. It is probable that the functional tests originated from the study of the faulty excretion of drugs giving rise to evidences of toxicity in certain diseases of the kidney. Various investigators (Todd<sup>10</sup> Charcot Roberts<sup>11</sup> Duckworth<sup>12</sup> Chauvet<sup>13</sup>) published accounts of the retardation in the excretion of various drugs among which may be mentioned Dover's powder mercury iodides alkaline carbonates salts of potassium and sodium quinine and salicylic acid. In 1877 Bouchard conceived the idea of using fuchsin for estimation of the excretory power of the kidney but little was accomplished until twenty years later when Achard and Castaigne<sup>14</sup> introduced methylene blue into the field and demonstrated the possibility of utilizing dyes in attacking this problem.

The work on osmotic pressure by Raoult and Van t Hoff was

applied as *cryoscopy* by Dreier,<sup>12</sup> Korányi,<sup>13</sup> Hamburger,<sup>14</sup> and Leon Bernard in studying the work performed by the kidney. The electrical conductivity of the urine was studied by Dawson Turner. "A blood of high resistance indicates that the proportion of salts in the blood is small or that the proportion of corpuscles present is large. Hence a high resistance of the blood but a low resistance of the urine is indicative of health." A hemorenal salt index—the ratio of the electrical resistance of the blood and urine was suggested.

The *methylene blue* test was introduced in 1897 by Achard and Castaigne.<sup>15</sup> The drug could be given by mouth in 1-grain doses but was usually administered by intramuscular injections, 15 minims of a 5 per cent solution.

this field

*Indigo-carmin* was used by Heidenhain<sup>16</sup> in his investigation of the physiology of the kidney. He concluded that the epithelial cells of the convoluted tubules were the portions of the kidney substance which excreted the dye. In 1903, Voelcker and Joseph proposed the use of the dye for the testing of renal function. The test was performed as follows: Twenty cc of a 0.4 per cent solution are injected into the muscles of the gluteal region. In stronger preparations the indigo-carmin does not remain in solution. A sufficient quantity must be used to give a deep color to the urine; the injection causes some pain and local irritation. In normal individuals the urine becomes tinged a greenish-blue ten to fifteen minutes after the injection, and subsequently becomes deep greenish-blue when good elimination occurs. According to Kapsammer,<sup>17</sup>

toxic and that albuminuria and convulsions had been induced. The next week the child died. The autopsy revealed a marked chronic interstitial nephritis. Fortunately, Dr. Thayer was present at necropsy and stated that the test had revealed the true nature of the disease and that the clinicians were forced to admit a mistake in diagnosis. This incident raised the value of the phthalein test considerably. Subsequent pathological studies by Dr. Thayer and Dr. Roy Snowden helped in attracting to it worldwide attention.

The normal or increased secretion of phthalein in certain cases of so called parenchymatous nephritis gave great concern. Pepper and Austin<sup>44</sup> and later W. Baetjer collected several cases of this type. The subsequent recognition of nephrosis as a separate type of renal disease clarified the situation. Today we realize that in cases of pure nephrosis the phthalein excretion is not diminished nor do urea and creatinine accumulate in the blood. Wilbur has recently reported a series of 32 carefully studied cases from the medical services of the Mayo Clinic in all of which the phthalein output was normal.

Geraghty and the author's first publication included over 200 functional tests on 150 subjects which seemed to justify the following conclusions: (1) Phenolsulphonephthalein is better adapted for a functional test than other drugs previously employed on account of its early appearance and the rapidity and completeness of its elimination by the kidney. (2) The quantitative estimation of the amount of drug excreted is simple and accurate. (3) The permeability of the kidney for this drug is decreased in chronic parenchymatous and chronic interstitial nephritis, the decrease being most marked in the interstitial variety. (4) The test has proven of practical value in revealing the true renal condition in cases with

the urinary  
surgeon  
functional

condition. (5) The test led to a striking improvement in the treatment of prostatic obstruction indicating those cases which need preliminary treatment before operation. (6) In unilateral and bilateral kidney diseases the absolute amount of work done by each kidney as well as the relative proportion can be determined when the urines are obtained separately.

The second communication corroborated the earlier conclusions and presented evidence indicating that (1) The absorption of phenolsulphonephthalein from the lumbar muscles is better than from the gluteal while the latter is superior to subcutaneous absorption. (2) Administration into the lumbar muscles is the method of choice. (3) Experimentally the diuretics which stimulate the renal cells to increased activity cause some increased secretion while those that act mechanically produce no increased secre-

tion clinically diuretics do not influence the phthalein output (4) Experimental evidence seems to indicate that phenolsulphonephthalein is excreted mostly by the tubules but probably also to a slight extent by the glomeruli (5) The renal cells display a striking specificity in the excretion of phenolsulphonephthalein (6) The test is of value from a diagnostic and prognostic standpoint in nephritis revealing the degree of functional derangement in nephritis whether of the acute or chronic variety (7) In the cardio-renal vascular cases the test has proved of value in determining to what degree renal insufficiency is responsible for the clinical picture

During this period Schlager and Hedinger<sup>53</sup> were attempting functionally to differentiate glomerular and tubular involvement and to classify the nephritides on this basis Schlager's methods interesting from an academic point of view have added little to the classification of the nephritides Dr Reginald Fitz Geraghty and the author<sup>54</sup> combined the phthalein studies with Schlager's tests the determination of lactose the salt and water tests and the potassium iodide test They concluded that the functional capacity of the kidney could be determined more accurately through these of the value sub-creted in cases of pure nephritis in response to sodium chloride stimulation was considered possibly of diagnostic value The potassium iodide test was found of little value The accumulation in the blood of incoagulable nitrogen in cases of nephritis was thought to be of great importance

### OTHER FUNCTIONAL TESTS

Urea and Its Determination In + + + + + + + +

in 1899

Great progress came from improvement of methods of study of urea and from Grehant's and later Ambard's studies of the laws of urea excretion (1912) Folin's method for the determination of non protein nitrogen was introduced (1912) and Marshall's urease

method for determining urea (1913) This was followed by a permanent urease preparation by Van Slyke and Cullen which further simplified the urea determination

Thereafter the work followed three main lines all pursued simultaneously (1) Estimation of blood urea and of non protein nitrogen in determining renal function (Marshall Rowntree and collaborators Folin etc) (2) Study of rate of excretion of urea (Ambard McLean Selling Addis and Watanabe Van Slyke and his collaborators) these resulted in Ambard's constant and in McLean's index and Van Slyke's urea clearance test (3) The rate of urea excretion after oral administration by Monakov Addis and Watanabe and McLean The method of choice relative to rate of urea excretion is in all probability the urea clearance test of Van Slyke representing one of the most accurate approaches to the determination of renal function In practice however the profession at present most extent on the simple determination of

An ingenious <sup>method</sup> <sup>was</sup> developed by Hench and Aldrich \* Recognizing the rather uniform distribution of urea throughout the tissues and body fluids they developed the salivary urea index whereby the urea of the saliva as determined by an extremely simple method indicates roughly the extent of urea retention in the body They also employed the mercury combining capacity of blood or serum as an index of urea retention in the blood

**Creatinine, Uric Acid and Sulphate Retention in the Blood —** Another important clinical test of renal function the estimation of the blood creatinine was introduced by Folin its clinical value being established largely through the studies of Myers and his collaborators Fine and Lough <sup>37-42</sup> It has proven of unusual value from the standpoint of prognosis in renal disease

of renal disease July 16, 1933

**Concentration and Dilution of the Urine in Indicating Renal Function —** Finally the urine itself affords a remarkable index of the

functional capacity of the kidney. From ancient times the variability of urinary excretion has been noted and discussed. Albarran,<sup>6</sup> in 1904, suggested that dilution response of the kidney to large

and determined the capacity of the kidney both to concentrate and to dilute. They placed their patients under rigid control and

and studies into general use. Addis and Stark<sup>7</sup> use as a functional test the concentration of the output in 24 hours.

#### Concentration and Excretion Coefficients and Renal Function.—

The use of mathematical formulas in determining the work done by the kidney permits more accurate statement of experimental findings, especially in relation to urea. This idea was introduced by Grehant,<sup>23</sup> brought into prominence by Ambard,<sup>7</sup> and into

of utilizing the curve of phthalein excretion, rather than the amount excreted for a given period of time was suggested and discussed by Geraghty and the author,<sup>20</sup> in 1910, and that normal curves for phthalein excretion following its intravenous injection were presented in 1912. At that time it was stated<sup>21\*</sup> "When intravenous administration is employed observations for more than one-half hour should not be used," the amount of excretion for this time being almost equal to that for two hours following the subcutaneous injection. This statement has been overlooked by some advocates of the urea-clearance test. The studies of Geraghty and the author, as published, indicated the phthalein output for the first one-half hour is 58 per cent and not, as has been intimated in certain studies, 55 per cent for two hours.

✓ Shaw<sup>24</sup>, of Miami, introduced a method for using the phenol-sulphonephthalein test somewhat analogous to the fractional analysis of gastric secretion. He determined the output at five- to ten-minute intervals on the curve or rate of excretion recovered in a specified period.

\* Quoted here because it has been so greatly ignored.



affords a more accurate functional test especially in prostatic hypertrophy. *Haberm* in the Mayo Clinic followed up this idea in a series of cases of enlargement of the prostate and his results concurred with Shaw's conclusions. In certain cases here the total output of phthalein is relatively high. The fractional determination allows additional information of great value.

If these two tests urea clearance and the phthalein output are to be compared it appears desirable to compare the curve or rate of phthalein excretion with the rate of excretion of urea. This is perhaps a challenge to those claiming a superior value for the rate of urea excretion over the phthalein test. Under any circumstances such a comparison seems highly desirable academically and clinically since the rate of excretion is probably the true index of the functional capacity of the kidney.\*

### CRITICISM OF FUNCTIONAL TESTS

Tests of renal function have been criticized. (1) Most frequently because they afford an index of the functional capacity at one particular time only and afford no clue as to the possibility of functional recovery. (2) It is said that the kidney does not excrete all substances with the same facility and that data obtained from the study of the elimination of one substance cannot be applied to others. (3) The functional test does not indicate whether the kidney is functioning at its normal rate or at or near its maximum. (4) In acute and in chronic parenchymatous nephritis functional tests seem to fail or at least give no adequate idea as to the severity of the renal condition. (5) Certain tests have been criticized because of the inaccuracy of colorimetric methods.

Despite these criticisms functional tests have come into general use and have proved of great importance in the practice of medicine. With several excellent tests available more than one test is usually employed in aiming at a decision. Repetition of the test gives information about changes in functional capacity both in medical and surgical diseases of the kidney. In the Mayo Clinic the phenol sulphonephthalein test is done first. If there is any indication or

\* Recently since this paper was written a comparison such as is here suggested has been carried out. The Fractional Phenolsulphonephthalein Test in Bright's Disease. C. H. R. H. A. Halsted (Am J Med Sc 1933 185 933)

suspicion of disturbance of renal function blood-urea determinations are made and, if these are strikingly abnormal, blood creatinine and occasionally blood uric acid are determined

### THE RÔLE OF THE PHTHALEIN TEST IN MEDICINE AND SURGERY

The phenolsulphonephthalein test is valuable in diagnosis, prognosis and treatment in both medical and surgical diseases of the kidney. On the medical side it is used to determine whether or not the kidney is actually involved in the disease process, in other words to determine whether disease of the kidney itself must be included or excluded. It is of importance in determining the nature of the renal lesion when such exists. In nephrosis, for instance the phthalein output is usually normal, occasionally increased. In late stages with contracted kidney and probably secondary nephritis the output may be considerably reduced. In diffuse glomerular nephritis excretion of phthalein is usually diminished and the degree to which it is decreased affords an index to the extent of involvement. This is true in both acute and chronic forms, but it must be kept in mind that in acute types the function may vary greatly within a short period of time. In focal nephritis, the phthalein output is rarely reduced. In the vascular types of nephritis the functional tests have been of unusual value, especially the determination of the phthalein output. In benign forms of hypertension, the phthalein output is normal and the urinary prof  
form  
the  
extr  
clinical condition. In cardiac disease, the state of the myocardium is often reflected in the renal function. During compensation the

This is particularly true in relation to digitalis therapy. In this connection the phthalein is a better indicator than the blood urea.

In certain forms of intoxication the phthalein output has played an important part in determining the involvement of the kidney. Thus in mushroom poisoning which was looked upon as a toxic psychosis a low phthalein output suggested renal injury and uremia was unmasked. In high intestinal obstruction, uremia is often encountered. The blood urea is high but the decrease in the output of the phthalein is a more specific index of renal injury. In polycystic kidney the phthalein output may be very low and the blood urea very high for long periods of time. In Addison's disease with

*falling circulation during the crises and end stages the urea of the blood increases and the phthalein output is decreased. This has been regarded as a toxemia of glandular origin but the decreased phthalein output indicates that it is secondary to renal insufficiency due in all probability to deficient renal circulation. In eclampsia the phthalein*  
 ■ a toxemia

*renal functional  
 its connection*

the total or combined renal function is the chief consideration. In addition information concerning the function of the individual kidney is highly desirable and at times essential.

In bilateral surgical diseases of the kidney, hypertrophy of the prostate is a common cause. Back pressure on the kidney leads to progressive decrease in renal function. This is indicated by the phthalein test but catheterization of the bladder is essential where urinary retention is present. As a rule where urinary retention is marked tests of blood retention are used by preference.

In the vast majority of cases the test by ordinary technique ■ employed. Attention has already been called to the superior value of the fractional test in certain cases where the output for the hour is near or within normal limits. In bilateral tuberculosis of the kidneys pyonephrosis pyelonephritis and multiple abscesses of the kidney the phthalein output indicates the degree of renal insufficiency. In hydronephrosis tests of retention afford a preferable index to function.

In unilateral diseases of the kidney the function of the individual kidney can be readily determined and on this surgical judgment and decision as to operation is based. In determining the function in the individual kidney the phthalein test excels except where difficulty is encountered in locating the ureteral orifice. Under such conditions chromocystoscopy ■ indicated and indigo-carmin is preferable. The phthalein test indicates the extent of injury of the diseased kidney and the capacity of the other kidney to carry

termination. Where renal diseases the phthalein output is determined by the kidney

phthalein test, the level of the test and Mosenthal's test

of concentration and dilution Tests of renal function reach their greatest value only when their findings are properly correlated with the history of the patient the physical findings the urinalysis

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## CHAPTER XIV

### THE BLOOD UREA CLEARANCE TEST

By ROGER R. HANNON, M.D.

**Introduction**—Since the earliest observations on Bright's disease there have been many methods devised to estimate the damage to renal function by measuring the urea in the blood and the rate of urea excretion in the urine. The blood-urea clearance test of renal function by Møller, McIntosh and Van Slyke was a logical development of the long course of observation, experiment and study by many investigators. These authors have described the development with

known as 'Studies of Urea Excretion' (see especially Van Slyke *et al.*<sup>1</sup>).

Van Slyke defines the term 'clearance' as *the volume of blood cleared of urea per minute corrected for urine volume when the latter is below 2 cc per minute*. The clearance is calculated from the observed urea concentration of the blood and urine,  $B$  and  $U$ , and the urine volume,  $V$ , in cubic centimeters per minute by the formulas

$$(1) C_m = \frac{UV}{B}$$

$$(2) C_s = \frac{U}{B} \sqrt{V}$$

The first is known as the *maximum clearance* and is used when the urine volume is 2 cc per minute and greater, or above the augmentation limit. The second is called the *standard clearance*. It expresses, for comparison, the value in terms of a standard constant urine volume output of 1 cc per minute. It has been found that below the augmentation limit the volume of blood, the urea content of which is represented in one-minute excretion, is not a constant, but varies, on the average, in proportion to the square root of the urine volume. It is practically impossible to fix the urine volume at a definite standard, but, by means of the square root rule of Austin, Stillman and Van Slyke,<sup>2</sup> the urea excretion that would accompany such a standard urine volume can be calculated from well as above illustrated by McIntosh and the following portion of

this portion represents expresses the average effect of urine volume changes below the augmentation limit. From the studies of Van Slyke *et al.*,<sup>8</sup> the mean maximum clearance for a person of average

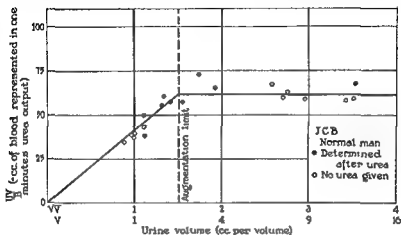


FIG. 39 — Urea excretion curve from normal subject

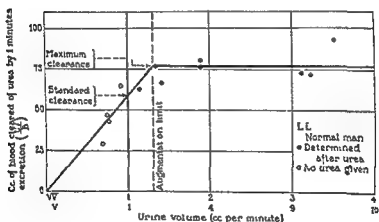


FIG. 40 — Urea excretion curve from normal subject

adult size is about 75 cc. of blood per minute and the mean normal standard clearance value is about 54 cc. of blood cleared of urea per minute. If these values are taken as 100 per cent, the per cent of normal renal function can be expressed by the calculations,



$1.33 C_m = \text{per cent normal (from } \frac{C_m}{75} \times 100)$ , or  $1.85 C_s = \text{per cent normal (from } \frac{C_s}{54} \times 100)$

The clearance in percentages of average normal values are therefore calculated as follows:

3 Percentage of average normal clearance =  $\frac{1.33 UV}{B}$  when  $V$  exceeds 2 cc of urine per minute

4 Percentage of average normal clearance =  $\frac{1.85 U \sqrt{V}}{B}$  when  $V$  is less than 2 cc of urine per minute

### THE VARIABILITY OF THE BLOOD-UREA CLEARANCE

Studies with this test have shown that in a given individual the probable variation of standard blood urea clearance is  $\pm 10$  per cent and that the maximum variation is much greater. Austin Stillman and Van Slyke have pointed out that this indicates that other factors in addition to blood urea concentration and urine volume affect urea excretion. Therefore an erroneous impression would be created by the clearance formulas if they were assumed to express with mathematical exactness the complete effects of all factors influencing urea excretion. Although the formulas only express the effects of two factors blood urea content and urine volume the limited range of normal variation indicates that they are ordinarily of chief importance in regulating the urea output.

It has been found necessary to standardize conditions in nearly all subjects. This is not  
 not subjected to any previous routine except that vigorous exercise is avoided and the previous meal should be a moderate one. The patient remains quiet while the urine is collected during two succeeding periods of one hour each. Inaccuracy in timing of urine collections and the incomplete emptying of the bladder are the chief sources of error. A few minutes before the end of the first hour a blood sample is drawn and its urea content is used for the calculation of the clearance for both hours. The use of two periods of urine collection serves to diminish the probability of undetected error from incorrect measurement of the collection period and from incomplete emptying of the bladder. Errors of either sort reveal themselves by discrepancies between the percentage of normal clearance found for the two periods. It has been found desirable to give the subject a glass of water to drink at the beginning of each of the two hours in order to obtain fairly rapid urine flow and thereby minimize the error from incomplete emptying of the bladder.

## CLINICAL OBSERVATIONS WITH THE CLEARANCE TEST

**Comparison of Range and Sensitivity of Test** — Under standardized conditions the variation in the clearance values of a normal individual due to other factors than those expressed in the formulas seems to be avoided to as large an extent as is possible. The values of 75 cc. of blood cleared of urea per minute for the maximum clearance and 54 cc. for the standard clearance have been taken as 100 per cent of normal function. However this does not mean that the kidneys cannot function at a higher rate of urea excretion or that 100 per cent is the maximum. In abnormal or pathological conditions values well above 200 per cent have been observed and this method has been found to be most accurate for estimating hyperfunction of the kidneys. Likewise there are conditions in which the kidney function is very low where the phenolsulphone phthalein is excreted in an unmeasurable trace but where the clearance can be measured repeatedly with remarkable accuracy. It has been of great interest to follow the course of Bright's disease in this low range where many tests lose their sensitivity. Van Slyke *et al.*<sup>6</sup> have compared the blood urea clearance with other measures of renal function. They have found that the blood urea clearance usually falls below 50 per cent of its normal value before the blood urea content, the blood creatinine and the phenolsulphonephthalein excretion show any abnormality. Only after the clearance indicates less than 20 per cent of normal renal function are all values for blood urea, creatinine content and for phenolsulphonephthalein excretion found outside the limits of normal variations.

**Acute Hemorrhagic or Glomerular Nephritis** Acute hemorrhagic nephritis is marked by the sudden onset of hematuria, proteinuria, edema and frequently diminished renal function, hypertension, plasma protein deficit and some anemia. During the first weeks of the acute stage it seems impossible to predict the outcome from the severity or mildness of any of these symptoms except plasma protein deficit. The renal function may be changed very slightly or it may be almost abolished but it does not appear that we can attach prognostic significance to the degree of early failure nor can we conclude that maintenance of normal renal function during the first months justifies either a good or bad prognosis. The author has had patients who during the second and third month after the onset of their illness have had renal function of only 5 to 10 per cent of normal and have shown uremic symptoms but have recovered either completely or to the latent stage. Other cases which have at first had but slight impairment of function and few subjective symptoms have shown a gradual loss of clearance progressing to the chronic and eventually to the terminal condition. In fact it is the author's impression that cases with insidious onset are

more likely to become chronic than those with a frank acute hemorrhagic onset. The interval from onset to attainment of recovery or of improvement to the latent stage in those cases which did not make a complete recovery varied from four to fifteen months. These have shown usually by the end of the fourth month improvement in their clearance values which except for an occasional slight setback has been continuous. The functional recovery has not always been complete even in some cases where subjective recovery made it impossible to keep the patient in the hospital. The author has not had an opportunity to observe many of these latent cases with function of 50 to 60 per cent of normal long enough to ascertain whether the partial functional loss was permanent. Later examinations in some cases have shown that the renal function has remained at this lower level for periods of two years others have shown further improvement after their discharge from the hospital. It has been of interest that cases which have recovered normal function and have passed through a period of hyperfunction may later have clearance values fixed at the lower limit of normal. Exacerbations associated with acute infections have occurred in patients who have had a temporary return of the clearance to normal range and in some instances the disease has taken on a progressive chronic character leading to uremia.

In all of the author's cases in which marked fall of the blood urea clearance occurred during the initial months and no definite tendency to rise was noted within four months after the onset progress downward to the active chronic or terminal stage followed. In the cases that have recovered or improved to the latent condition the clearance has either remained normal during the initial stage or has begun to rise within four months after onset.

The essential for a good prognosis therefore is that within four months after the acute onset the clearance—if it has fallen—will have

patients who have  
the onset and still  
have shown no tendency to improve while kidney function has  
remained fixed or more often has slowly decreased have been  
considered as chronic active cases of hemorrhagic nephritis. There  
have been periods of several months or even more than a year  
when the progress of the disease was arrested. There have been  
periods when subjectively and clinically a patient appeared so  
improved and felt so well that he has returned to his occupation  
and active life but the clearance during this time has shown that  
there was a gradual loss of function. This loss in some cases was  
rapid and in others slow but when it has fallen to 20 per cent or  
less they have been considered in the terminal stage.

## Terminal Hemorrhagic Nephritis — With the fall of the clearance

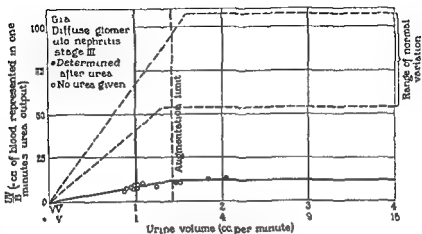


FIG. 41 — Urea clearance curve from patient with diffuse glomerulonephritis Stage III

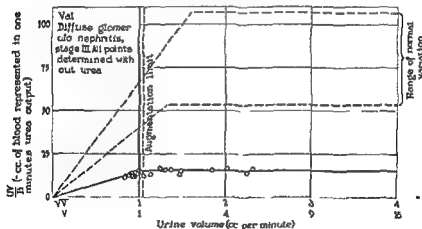


FIG. 42 — Urea clearance curve from patient with diffuse glomerulonephritis

retention and a decrease of proteinuria. He changes from the 'wet nephritis' to the non-edematous, pre-uremic terminal stage. The patient rid of the annoyance of the edema, is likely to feel improved and may be able to leave his bed for the first time in months. Such

a change is not so obvious in those cases that have a rapid downward course. Sometimes edema continues, or nephrotic edema is replaced by cardiac edema. After the clearance has fallen permanently below 20 per cent of normal, survival has been less than one year in 60 per cent of the author's cases, one to two years in 30 per cent and over two years in only 10 per cent. With the loss of functional elasticity the urea clearance becomes very steady at this time and one can often follow, per cent by per cent, the further failure of the urea secreting ability. When there remains but 5 per cent of the normal renal function, uremia appears to be inevitable. By very careful nursing and dieting, the unpleasant symptoms may still be avoided for a time, but any exertion, shock or indiscretion may bring on uremia and coma.

Figures 41 and 42 show the uniformity of the clearance values obtained on 11 patients in the terminal stage. These figures also suggest the futility of forcing fluids above the augmentation limit in order to clear the blood more rapidly of urea.

**Nephrosis or Degenerative Bright's Disease**—The author has classified as nephrosis or degenerative Bright's disease those cases which have had an insidious onset, marked edema and proteinuria, marked lowering of the plasma proteins without hypertension and without hematuria. He has gone most carefully into the history of each patient for evidence of former renal disease, history of hematuria, infections, etc. in order to rule out, if possible, those individuals who are in the latent or chronic active stage of hemorrhagic nephritis with the nephrotic syndrome. Careful urine examinations were made microscopically to assure him that the sediment indicated a degenerative rather than an inflammatory lesion. The majority of the cases have shown decreased urea clearances. Some have shown periods of hyperfunction. Two cases have progressed to uremia, urea retention and hypertension. At autopsy their kidneys were found to be small and scarred with great destruction of the glomeruli. Another case, reported by MacKay and Johnston<sup>2</sup> of sixteen years duration showed very slight lowering of clearance values. This patient died with streptococcus peritonitis and the kidneys were the large, pale yellow type usually associated with lipoid nephrosis. Even in this case many of the glomeruli were destroyed. It appears therefore, that a gradual decrease of urea excreting ability frequently develops during the course of so-called nephrosis and that the disease may end in uremia, the glomeruli then being involved.

**Arteriosclerotic Bright's Disease**—This disease is characterized by a gradual decrease in urea clearance over a period of years. The fall of the clearance marks the advent of uremic symptoms. The fall of the clear-

ance in some cases is gradual over a period of years. Other cases may go for a long time with little decrease in clearance, and then show a rapid drop to the uremic level within two or three months. At the time of death the more outstanding symptoms may be cardiac, even when the low clearance shows such complete renal failure that a fatal outcome from this cause could not have been long avoided.

**Summary**—Observations carried on during the past ten years lead to the following conclusions:

In *chronic* Bright's disease a steady fall in the urea clearance

or sclerotic type

In *acute* Bright's disease on the other hand the clearance may fall to nearly the uremic level and nevertheless recovery may occur. Such recovery is rare however unless the clearance begins to rise within four months after the onset.

A normal clearance does not necessarily prove the absence of renal disease. In cases recovering from the hemorrhagic or degenerative disease the clearance may regain a normal level while one or more other signs such as microscopic hematuria, albuminuria or edema persist. Such a case cannot be considered to have recovered. Usually if the clearance regains normality disappearance of other signs of renal pathology occurs at the same time or later. But sometimes complete healing never occurs, the disease becomes chronic and the clearance shrinks again. This time the shrinkage indicates irreversible destruction of glomeruli.

Examples of the progress of the urea clearance in different types of the disease are shown in a monograph covering 66 charted cases.\*

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## CHAPTER XV

### STUDIES IN REHBERG'S CREATININE TEST FOR GLOMERULAR FILTRATION \*

By GRACE MEDES Ph D AND HILDING BERGLUND, M D  
(IN PARTIAL COLLABORATION WITH E BLEGEN M D)

#### DETAILED STUDIES OF RENAL BEHAVIOR

IN the case of creatinine the direct relation, which generally exists between the concentration of a substance in the plasma and the amount eliminated in the urine is subject to fewer conditions than most urinary constituents. This holds not only in comparison with substance like chlorides, uric acid, phosphates and calcium, for which the conditions governing elimination are admittedly complicated, but also in comparison with urea, whose elimination has been more extensively studied than any other urinary constituent. The important phenomenon justifying this statement is the independence of creatinine excretion and urinary volume. It has been possible so to arrange conditions that they permit the use of the creatinine con-

difficult or impossible to prove, but the reasoning is supported by the facts that creatinine is concentrated more than any other urinary substance (Rehberg) and the excretion ratio  $\frac{\text{urine rate}}{\text{plasma concentration}}$

for creatinine higher

amounts to the same,  $\frac{\text{urine rate}}{\text{plasma concentration}}$

ion between plasma  
ly even the maximal

value for plasma creatinine is of such a small magnitude that it is inadvisable to base calculations on its variations. Since the early work of Folin the rate of normal creatinine excretion has been correlated with body weight. Eliminating variations in normal plasma creatinine from the calculations, one arrives at the correlation of

\* Aided by a grant from the research fund of the Graduate Medical School of the University of Minnesota.

normal creatinine excretion with body weight and with the magnitude of glomerular filtration. We shall later submit this view to a statistical test.

Rehberg<sup>21</sup> found the creatinine excretion to vary roughly with the creatinine content of the plasma, while MacKay<sup>20</sup> so arranged the conditions that he obtained complete proportionality between excretion and plasma concentration. The authors present a few examples of reactions given by different individuals. For the sake of simplicity they first present the response of a diseased kidney.

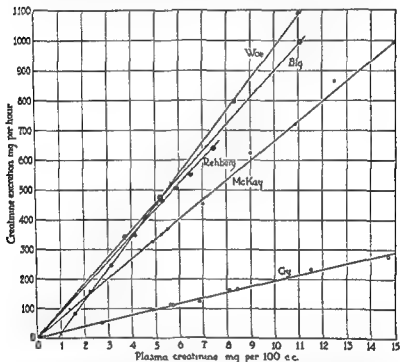


FIG. 43.—Ratio of creatinine excretion to plasma creatinine in *Gy*, a patient with highly inefficient kidneys, and *Woe* and *Blq*, two individuals with normal kidneys. The curves of McKay and Rehberg have been introduced from their respective data (McKay<sup>20</sup> and Rehberg<sup>21</sup>).

Table 15 and curve *Gy* in Fig. 43 represent the results of a series of observations on a man, aged twenty-eight years, with primary hypertension. The functional capacity of his kidney is reduced 80 per cent or more. The plasma creatinine varied from 2.73 mg without any creatinine being given, to 14.7 mg per 100 cc. The creatinine excretion in this series of observations



depends upon no other factor than the plasma creatinine concentration. The patient had for weeks been in recumbant position, the blood-pressure remained unusually constant at a high level. The glomerular filtration per minute is independent of the plasma creatinine level and practically constant, varying between 30.7 and 33.5 cc only. This means that the ratio  $\frac{\text{excretion (hour)}}{\text{plasma creatinine}}$ , as used by MacKay is also constant, varying between 18.4 and 20.1 only. When plotted against plasma creatinine the rate of excretion is expressed by a straight line originating from the zero point. Two

TABLE 15.—MINUTE FILTRATION AND CREATININE EXCRETION AT DIFFERENT LEVELS OF PLASMA CREATININE

SUBJECT Mr. G. y. Aged twenty-eight years Primary hypertension

Creatinine ingested	Time	Plasma creatinine mg per 100 cc	Creatinine excretion mg per hr	Minute filtration cc	Excretion (hour) plasma creatinine
3 gm	2.21	7.5	163.0	33.5	20.1
		8.7			
3 gm	3.6	2.75	110.7	32.6	19.6
	6.30 A.M.	8.55			
	10.00 A.M.	8.55	165.9	32.8	19.7
	1.00 P.M.	8.28			
3 gm	1.00 P.M.	8.28	231.0	32.6	19.6
	1.30 P.M.	14.70			
	2.45 P.M.	14.70	226.5	31.2	19.7
	2.45 P.M.	14.70			
	3.45 P.M.	14.70			
	3.7	6.84	126.1	30.7	18.4
	9.50 A.M.	6.84			
	11.00 A.M.	5.70	110.0	33.1	19.3
	3.00 P.M.	5.70			
0	3.16	2.73	50.0	30.8	18.5
	8.00 A.M.	2.73			
	9.00 A.M.	2.73			

facts lend particular significance to these determinations. The determinations constitute three separate experiments covering four days and spread over twenty-four days. During this period there was no noticeable variation in the mode or extent of the renal function in this individual. The second point to call attention to is that the lowest plasma creatinine determination was 2.7 mg only, before any creatinine had been given. Even under this condition the law governing the creatinine excretion remains unmodified.

At this point it becomes necessary to discuss the significance of the plasma creatinine values obtained when no creatinine has been ingested. Rehberg touches lightly upon this question, avoiding

mination. It is worth while to recall the story of the preformed blood creatinine excellently told by Hunter<sup>18</sup>. It was found that the so-called preformed creatinine of whole blood reduced picric acid at a different rate from the standard made up from purified creatinine doubt thus being thrown upon the practical specificity of this admittedly unspecific reaction. Hunter and Campbell<sup>19</sup> showed that this objection was not valid for the plasma creatinine which they consequently accepted as true creatinine. Behre and Benedict<sup>2</sup> on the basis of the irregular behavior of whole blood creatinine toward heat and sodium hydroxide and toward kaolin concluded that preformed creatinine was not present in the blood in appreciable amounts. Though no other explanation of the interesting observations of Behre and Benedict seems to have been given their conclusion was disproven by Gaebler and Keltch<sup>14</sup> by the isolation of preformed creatinine from both normal and nephritic blood. Though there is little reason to assume that the isolation was quantitative it is important that their isolated material corresponded to about 0.4 mg. creatinine per 100 cc. normal human blood and in nephritics to about one half of the amount colorimetrically determined. In the authors' experiment the patient with reduced renal function presented an elevated plasma value for preformed creatinine of 2.7 mg. per 100 cc. a doubling of the normal value.

Referring back to curve *Gy* in Fig. 43 or to Table 15 we are unpresaged with the mathematical precision of the correlation between output and plasma concentration. Assuming the value before the ingestion of creatinine as well as all subsequent values to be 1.35 mg. too high the curve would move up and reach the zero point for plasma creatinine at an excretion of about 30 mg. creatinine per hour. This would necessitate the assumption of an active secretion of creatinine. Considering the curve where it actually is as the more likely expression of what takes place it is necessary to assume either that both plasma and urine values are correct expressions for the true preformed creatinine or that the other compounds or compounds which besides creatinine go to make up the total picric acid reducing plasma content are eliminated at the same rate as creatinine.

medical  
results

are atypical but clear-cut. The authors have carefully looked into the physical condition of their subject on repeated examinations in the students' health service. He was found always to have a low blood pressure about 100/60. Observations are made up of six

TABLE 16—MINUTE FILTRATION AND CREATININE EXCRETION AT DIFFERENT LEVELS OF PLASMA CREATININE

SUBJECT Mr Wee Aged twenty two years Healthy student

Creatinine ingestion	Time	Plasma creatinine mg per 100 cc	Creatinine excret on mg per hr	Minute filtration cc	Excretion (hour) plasma creatinine	
10 gm	10 00 A M					
	11 00 A M	11 07	1094	167	100 0	
	12 00 M	10 08				
	1 00 P M	9 00	799	160	95 9	
	2 00 P M	7 65				
	3 00 P M	6 12	523	153	91 6	
	4 00 P M	5 28				
	4 00 P M	5 28	457	130	90 1	
	5 00 P M	4 86				
	5 00 P M	4 86	408	149	89 6	
6 00 P M	4 24					
3 gm		3 63	349	141	84 5	
		4 62				
2 gm		3 48	246	131	78 6	
		2 79				
1 gm		2 46	159	115	70 0	
		2 08				
0		1 56	84	90	53 8	
Diuresis cc /hr						
0	67	9 10 A M	1 39	71	86	51 4
40 gm urea	96	10 10 A M	1 38	72	87	52 1
	528	11 10 A M	1 38	76	91	55 1
	240	12 10 P M	1 44	64	74	44 4

different tests, performed on different days, without creatinine and after the ingestion of 1, 2, 3 and 10 gm, respectively. The plasma creatinines thus were made to vary from 1.4 to 10.9 mg. The elimination rate presents a straight-line relationship, but the curve reaches the zero point for elimination before the zero point for plasma concentration. In other words, the ratio between elimination and plasma concentration is modified by another factor, which we believe to be the filtration rate or volume. In this subject it, therefore, appears that the filtration rate is influenced by the plasma-creatinine concentration. The glomerular minute filtration rose from 86 to 167 cc, step by step, as the plasma creatinine level rose. Table 16 makes clear that this change in minute filtration is not a gradual process as far as time is concerned, the different

of simultaneous

in Fig. 43, the  
corresponding to

from each plasma creatinine value, moving the curve to the left and starting it from zero, it becomes identical in character with the previous curve,  $G_y$ , with a constant filtration-rate of 179 cc per minute. Thus there is not believed such "corrections". The reasons why they consider such a correction unjustified are partly evident from the discussion of the first experiment.

10 gm, respectively. During the second hour after the ingestion of 2, 3 and 10 gm creatinine, Dr Blegen responded with what under

TABLE 17—MINUTE FILTRATION AND CREATININE EXCRETION AT DIFFERENT LEVELS OF PLASMA CREATININE

SUBJECT Dr Blegen Aged twenty-eight years

Creatinine ingestion	Time	Plasma creatinine mg per 100 cc	Creatinine excretion mg per hr	Minute filtration
10 gm	6-14			
	7 00 A M			
	9 00 A M	10.34	11.07	906.8
	10 00 A M	11.40		
	11 00 A M	8.71	5.04	616.0
	12 00 M	7.74		
	1 00 P M	6.96	6.75	419.0
	2 00 P M	6.54		
	About for one and a half hours			
	4 30 P M	3.78	3.78	253.0
	5 30 P M	3.78		
2 gm	6-13	3.00	3.74	340.5
		4.34		
1 gm	6-11	3.11	2.99	161.3
		2.53		
0	6-6	1.575	73.0	77.3
0	5-29	1.575	75.2	79.5
0	5-24	1.575	68.6	72.6
3 gm	5-27	5.30	5.21	474.8
		5.12		

the circumstances appears as his maximum filtration 1547 cc  
1534 cc and 150 cc minute filtration The corresponding plasma  
s follows 37 mg 52 mg  
cretion rates per hour are  
plotted against the plasma  
concentrations are accurately placed upon the straight line *Bfg*  
(Fig 43) originating from the zero point It shall again be empha  
sized that each point represents a separate experiment

Rehberg<sup>7</sup> published a self-experiment the first part of which (Rehberg Fig. 43) during four separate determinations showed a complete proportionality between rate of elimination and plasma creatinine the straight line laid over the separate points originating from zero. The range of the plasma creatinines in this part of Rehberg's experiment was not great 5.3 to 7.45 mg only. The range was decidedly greater in Machay's experiment referred to above (Machay Fig. 43).

Summarizing this part of the experiment it is evident that in some but apparently not in all subjects under certain conditions the creatinine excretion is completely proportional to the creatinine concentration of the plasma. The curves originating from the zero point in Fig. 43 could hardly have been obtained unless the methods for the creatinine determinations in plasma and urine determined essentially or proportionally the same substance or substances in both fluids. This conclusion renders support to the assumption that the normal values for preformed plasma creatinine are essentially correct.

The authors second experiment curve *Wce* showed that even with a straight line relationship between elimination and plasma concentration a second factor might influence the elimination namely the rate of filtration. Ordinarily changes in filtration rate cause a deviation from the straight line relationship (fig 44). This leads to a discussion of the factors which influence the rate of filtration. We have attempted to study the following factors blood pressure rate of blood flow and plasma-creatinine concentration. The latter we have studied more extensively than the others. In normal individuals high filtration rates were not observed without ingestion of creatinine. Repeated tests without creatinine separated by weeks or months but on the same individual have given practically identical rates. Patients with incompetent kidneys (Table 15) frequently show maximum filtration without creatinine ingestion. Normal individuals upon ingestion of creatinine show not necessarily a maximum filtration but a high filtration constant from one test to another. The minimum amount of creatinine necessary varies. A constant filtration rate was not obtained after 1 gm creatinine. After 3 gm the results have varied. Dr Blegen reached his constant high value after

2 gm, while Dr Mn did not. After 3 gm creatinine, the authors obtained the same filtration as after 10 gm. Three grams were,

in the ninth hour after the subject had been active in the wards for one to two hours. In Dr Mn, after 3 gm, the rate likewise fell in the third or fourth hour. These drops in filtration rate are independent of the level of the plasma creatinine.

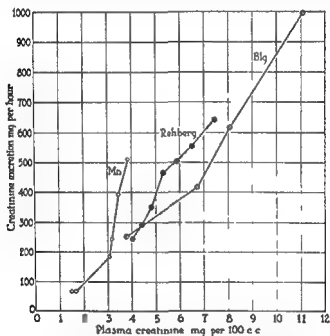


FIG. 41.—Ratio between creatinine excretion and plasma creatinine level in Blg and Mn two normal interns showing high ratio immediately following ingestion of creatinine with subsequent variations after different time intervals.

### STATISTICAL STUDIES IN NORMAL VALUES

Under standard conditions  $\kappa_{12}$  during the second hour after ingestion. Rehberg 113 as below normal limits.

The authors have determined the minute filtration under the same standard conditions in 60 normal medical students and interns, none of whom showed albumin or pathological sediment in the urine

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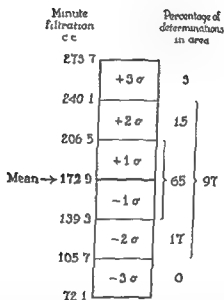


FIG. 45.—Minute filtration (creatinine clearance) of 60 normal medical students after ingestion of 11 gm. of creatinine showing the range of clearances included in  $\pm 1$   $\sigma$  and 3 times the standard deviation together with the percentage of areas in each area.

The range of the minute filtration extended from 111 to 253 cc, with a mean value of  $172.9 \pm 2.9$ . The standard deviation ( $\sigma$ ) was  $33.6 \pm 1.1$ . Figure 45 depicts the areas covered by plus or minus one, two and three times the standard deviation, with the percentage of determinations contained in each area. Sixty five per cent of all determinations fall within plus or minus once the standard deviation and 97 per cent within plus or minus twice the standard deviation.

No definite correlation existed between minute filtration and body weight and no correlation between filtration and plasma creatinine level. The basis for the former statement is as follows:

The mean weight was  $153.35 \pm 1.74$  pounds, with a standard deviation of 19.93 pounds. The coefficient of correlation of weight and filtration was  $+0.28 \pm 0.12$ , giving a ratio of the coefficient of correlation to its probable error of 2.34, rendering the coefficient of doubtful significance. The mean value of the plasma creatinine was  $4.24 \pm 0.06$  mg. The coefficient of correlation of plasma creatinine and filtration was  $+0.05 \pm 0.12$ , with a ratio between the two of 0.4.

The authors have further determined the minute filtration without previous administration of creatinine in 35 normal students, some of whom had the 3 gm. test too. The findings are depicted

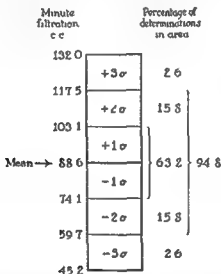


FIG. 46.—Minute filtration (creatinine clearance) of 34 normal medical students with no previous creatinine ingestion, showing the range of clearances included in  $\pm 1$  and  $\pm 2$  times the standard deviation, together with the percentage of cases in each area.

in Fig. 46. The range of minute filtration lay between 55 and 120 cc. with a mean value of  $88.6 \text{ cc} \pm 1.6$ . The standard deviation ( $\sigma$ ) was  $14.5 \pm 6.9$ . Sixty-three per cent of all values lay within plus and minus once the standard deviation and 94.8 per cent within twice the standard deviation. The 1 $\sigma$  mean was 88.6 cc.

early in this chapter, the twenty-four hours' creatinine excretion



shows a high positive correlation who received no creatinine relation between weight and correlation being  $+0.58 \pm 0.11$  the ratio between coefficient and probable error being 5.45. As already stated no such correlation existed after the ingestion of creatinine.

The interpretation of the vastly different filtration rates without and with creatinine must remain tentative. It is evident from the earlier discussion that the authors are not inclined to ascribe

one situation but not in the other. Little objection should be raised against the interpretation that the filtration rate when no creatinine has been ingested represents all that is needed to meet the excretory demand when no extra load has been imposed and that the higher rate after ingestion of creatinine represents the maximum filtration occurring in immediate response to stimulation of glomerular structures by normal metabolites\*. The varying filtration rates depicted in Fig. 44 demonstrate the almost continuous variations which occur in the course of a day independent of the plasma creatinine level after the first stimulation has worn off. Note particularly curve *Mn* in which the filtration is independent of the plasma creatinine is exemplified.

The authors have attempted to demonstrate the effect of increased blood flow upon the filtration rate. In 20 determinations on 18 patients with clinically well-developed hyperthyroidism (Blumgart) the filtration rate after 3 gm creatinine was determined. The material included new untreated cases as well as cases of long standing which had been treated with varying degree of success. The basal metabolic rates given in Table 18 represent the determinations nearest the day of the creatinine test varying from one day to two weeks. The patient with the metabolic rate of  $-2$  a white male is an old case formerly very severe with persisting eye symptoms. All patients showed normal urine.

The range of minute filtration extended from 111 to 338 cc which is 85 cc wider than in the normal material. The patient with the filtration rate of 338 cc was a young man in a very toxic condition untreated presenting a basal metabolic rate of  $+73$ . After twenty-one days of Lugol treatment his metabolic rate had dropped to  $+12$  and his filtration rate to 277 cc. As shown by

Table 18 15 out of the 20 values fell above the normal mean, 2 values between plus once and twice the standard deviation 3 between +2 and +3 times the standard deviation 1 between +3 and +4 times the standard deviation and 1 beyond +4 times

TABLE 18—FILTRATION RATES IN HYPERTHYROIDISM

Relat on to normal mean		Subj ect	Basal cre atin in e rate	Plasma cre atin in e mg per 100 cc	Creat in e excret on mg per hr	Mo du e fil at on cc
+4σ	5654 <sup>9</sup>	Mr E H	+73	3 17	674	337 5
+3σ		Mr E H	+12	3 73	559	277 3
	97399	Mr F N	+106	4 14	656	264 2
	59744	Mrs M H	+7 <sup>9</sup>	3 31	490	245 3
+2σ	57070	Mrs b D	+35	3 31	445	243 4
	51434	Mr C D C	-2	5 43	636	217
+1σ	44509	Mrs M H	+3	4 00	516	16 0
	57070	Mrs S H	+36	3 65	390	149 0
	56477	Mr A A	+7 <sup>9</sup>	4 14	219	178 3
	5 719	Mrs E H	+75	2 73	10	174 2
	507 06	Mrs L T	+36	4 14	442	174 4
		Mrs K H	+33	4 0	4 0	174 6
	89 95	Mr P B	+14	5 40	571	174 3
	56 136	Mrs M J	+	5 75	600	173 7
M	59375	Mrs H L	+1 <sup>9</sup>	3 66	340	174 7
	560 4	Mrs S C	+25	5 91	643	168 8
-1σ	4856 <sup>9</sup>	Mrs I L	+30	5 67	547	160 1
	5 1769	Mrs F M	+18	5 46	475	159 1
	5 6477	Mrs G H	+44	5 70	474	155 1
σ	56306	Mrs M C	+25	5 08	540	141 2

elevated filtration. We present our unselected material.\* The material further shows one peculiarity not present among the normals, viz a significant negative correlation between plasma creatinine and filtration rate the coefficient of correlation being  $-0.12 \pm 0.1$  the ratio between the coefficient and its probable error being 0.5. The plasma creatinines varied between 2.73 and 7.05 mg per 100 cc the mean being  $4.51 \pm 0.18$ . There was no significant correlation between plasma creatinine and creatinine excretion the coefficient of correlation being  $+0.16 \pm 0.11$ . This fact is surprising remembering that in the experiments recorded

\* Our material consists of 13 women and 5 men. The mean filtration of a 5 cc determination on the men is 1.35 cc.

shows a high positive correlation who received no creatinine relation between weight and correlation being  $+0.58 \pm 0.11$  the ratio between coefficient and probable error being 5.45. As already stated no such correlation existed after the ingestion of creatinine.

The interpretation of the vastly different filtration rates without and with creatinine must remain tentative. It is evident from the earlier discussion that the authors are not inclined to ascribe

raised against the interpretation that the filtration rate when no creatinine has been ingested represents all that is needed to meet the excretory demand when no extra load has been imposed and that the higher rate after ingestion of creatinine represents the maximum filtration occurring in immediate response to stimulation of glomerular structures by normal metabolites\*. The varying filtration rates depicted in Fig. 44 demonstrate the almost continuous variations which occur in the course of a day independent of the plasma creatinine level after the first stimulation has worn off. Note particularly curve *Mn* in which the filtration's independence of the plasma creatinine is exemplified!

The authors have attempted to demonstrate the effect of increased

material included new untreated cases as well as cases of standing which had been treated with varying degree of success. The basal metabolic rates given in Table 18 represent the determinations nearest the day of the creatinine test varying from one day to two weeks. The patient with the metabolic rate of  $-2$  a white male is an old case formerly very severe with persisting eye symptoms. All patients showed normal urine.

The range of minute filtration extended from 111 to 338 cc which is 85 cc wider than in the normal material. The patient with the filtration rate of 338 cc was a young man in a very toxic condition untreated presenting a basal metabolic rate of  $+73$ . After twenty one days of Lugol treatment his metabolic rate had dropped to  $+12$  and his filtration rate to 277 cc. As shown by

Table 18, 15 out of the 20 values fell above the normal mean, 2 values between plus once and twice the standard deviation, 3 between +2 and +3 times the standard deviation 1 between +3 and +4 times the standard deviation and 1 beyond +4 times

only to select a group of hyperthyroid cases showing a significantly

TABLE 18—FILTRATION RATES IN HYPERTHYROIDISM

Relation to normal mean	Subject	Basal metabolic rate	Plasma creatinine mg. per 100 cc.	Creatinine excretion mg. per hr.	Minute filtration cc.
+4σ	5654 <sup>9</sup> Mr E H	+73	3.1 <sup>~</sup>	624	337.5
+3σ	Mr E H	+12	3.3 <sub>5</sub>	559	277.3
+2σ	97309 Mr F N	+106	4.14	656	264.2
	56744 Mrs M H	+3 <sup>7</sup>	3.83	490	215.3
	5 <sup>00</sup> 0 Mrs S D	+35	3.43	445	213.4
+1σ	51434 Mr C D C	-3	5.43	630	247
	41504 Mrs M H	+5	4.00	515	160
M	5 <sup>00</sup> 0 Mrs S H	+30	3.6 <sub>5</sub>	300	159.8
	5 <sup>0</sup> 27 Mr A A	+9	4.14	219	175.5
	54 <sup>19</sup> Mrs E H	+34	4.75	107	176.2
	507 <sup>00</sup> Miss L T	+30	4.14	419	177.4
	Mrs K H	+33	4.02	470	174.6
	59 <sup>09</sup> 3 Mr P B	+14	5.46	571	174.9
	5 <sup>0</sup> 136 Mrs M J	+7	5.75	610	173.7
	583.5 Mrs H L	+4 <sup>0</sup>	3.60	340	172.7
	50 <sup>0</sup> 24 Mrs S C	+95	5.94	641	166.6
	48 <sup>0</sup> 42 Mrs I L	+10	5.67	547	160.1
-1σ	5.1309 Mrs F M	+14	5.46	475	123.1
σ	5.087 <sup>0</sup> Mrs C H	+44	5.70	474	125.1
	56506 Miss M C	+2 <sub>5</sub>	4.04	440	111.2

elevated filtration. We present our unselected material.\* The material further shows one peculiarity not present among the normals viz a significant negative correlation between plasma creatinine and filtration rate, the coefficient of correlation being  $-0.62 \pm 0.1$  the ratio between the coefficient and its probable error being 6.5. The plasma creatinines varied between 2.75 and 7.05 mg per 100 cc. the mean being  $4.51 \pm 0.18$ . There was no significant correlation between plasma creatinine and creatinine excretion the coefficient of correlation being  $+0.16 \pm 0.16$ . This fact is surprising remembering that in the experiments recorded

\* Our material consists of 13 women and 5 men. The mean filtration of six liter infusions on the men = 15 cc.

in Table 15 and in curve *Gy* of Fig 43 the correlation is complete. An inspection of Table about as often by low high plasma creatinine found in hyperthyroidism as the abnormally or unusually high filtration-rates and the frequent independence of plasma creatinine and creatinine excretion are to be ascribed to increased blood flow alone as we anticipated or whether other factors too have to be considered must be left unanswered. As one such factor one might suggest an abnormal relaxation of the glomerular capillaries. Table 19 compares the mean filtrations.

TABLE 19 — MEAN GLOMERULAR FILTRATION

Condition	No. of tests	Mean	Standard deviation ( $\sigma$ )	Coefficient of variability
Normal no creatinine	38	88.6 $\pm$ 1.6	14.5 $\pm$ 1.1	16.3
Normal after 3 gm creatinine	60	17.9 $\pm$ 2.9	33.6 $\pm$ 2.1	19.4
Hyperthyroidism after 3 gm creatinine	70	196.0 $\pm$ 8.6	55.8 $\pm$ 6.0	28.4

## OBSERVATIONS ON PATHOLOGICAL KIDNEYS

The basis for the following analysis is 86 separate tests on 82 different individuals the youngest being fourteen years of age the others all being adults. All presented some urinary pathology. Most types of diffuse renal lesions are represented. orthostatic albuminuria is also present. No surgical renal conditions have been included. The material has been divided into five groups as follows. Group I includes 42 tests with filtration rates above 100 cc. Group II includes 14 filtration rates from 51 to 100 cc. Group III 13 rates from 21 to 50 cc. Group IV 11 rates from 11 to 20 cc. and Group V 8 rates below 11 cc. The lowest rate was 0.51 cc per min per 100 cc blood. The highest was 260 cc in a youth recovering from acute nephritis. The mean filtration in Group I was 155 cc  $\pm$  4.7 the standard deviation was 45.7 cc the mean value being 18 cc less than the normal mean but the standard deviation 12 cc larger. The difference between the means lacks statistical significance. The means of the other groups given in Table 20 are dependent on the arbitrarily chosen group limits.

The relation between non protein nitrogen and filtration rate will be discussed first. This necessitates a review of the limits of normal non protein nitrogen. Berghlund<sup>4</sup> in Folin's laboratory, in 12 young

...le (laked) blood with 28 Folin and Svedberg<sup>17</sup> in f 31 mg (maximum and minimum 33 and 26 mg, respectively) before breakfast and 31 mg (maximum and minimum 42 and 26 mg, respectively) two and a half hours after breakfast. The authors possess a series of values from 19 normal individuals, physicians and technicians around the laboratory, within the age of twenty-two to fifty-five years. No blood sample was drawn on a fasting stomach. The values fall between 23 and 40 mg, with a mean of  $32 \pm 0.7$ . Our continued experience with fully normal individuals confirms the correctness of these narrow limits for normal non-protein nitrogen.\*

TABLE 20.—SUMMARY OF THE PATHOLOGICAL MATERIAL

Group	No. of observations	Mean filtrate per min.	Mean plasma creatinine mg per 100 cc.	Mean $\frac{N}{P}$ $\frac{N}{P}$ mg per 100 cc.	Difference of means prob. error of difference
Normal 3 gm. creatinine	60	$172.9 \pm 2.9$	$4.24 \pm 0.06$	$3.0 \pm 0.7$	6.3 2.8 — 3.0 3.4 5.2
Abnormal kidneys I Filtration 101 cc.	42	$154.8 \pm 4.7$	$5.21 \pm 0.14$	$3.0 \pm 0.6$	
II Filtrate on 51-100 cc.	14	$76.8 \pm 2.5$	$6.65 \pm 0.19$	$4.10 \pm 1.1$	
III Filtration 1-50 cc.	13	$73.6 \pm 1.7$	$6.4 \pm 0.13$	$5.19 \pm 2.4$	
IV Filtration 11-50 cc.	9	$17.0 \pm 0.4$	$9.66 \pm 0.7$	$7.13 \pm 4.2$	
V Filtration 10 cc.	8	$5.4 \pm 0.7$	$12.30 \pm 1.1$	$16.0 \pm 17.0$	

... of individuals with diseased kidneys who possess a filtration rate between 10 and 100 cc. and a non-protein nitrogen of

$30 \text{ mg} \pm 0.8$  which is significantly higher than the normal mean. The ratio between the difference of the means and the probable errors of the means being 6.3. There is no definitely significant difference in mean non-protein nitrogen between the group with filtration rate above 100 cc. (I) and the group with filtration between

\* The variability of normal blood urea was studied by Mackay and Mackay (1924) and found to be 1.5 to 2.5 mg per 100 cc. in different individuals. Compare last paragraph of our discussion and summary.



tive freedom. The ratio thus might give a different picture of altered function (Table 21). For the first time in this study we here meet with a marked difference in behavior between the normals and the subjects of Group I, the median value of the concentration ratio of the latter being only slightly higher than one-half the normal ratio. The drop in the ratio is gradual through Groups I to III and differs in this respect from the plasma creatinine and non protein nitrogen but corresponds roughly with the filtration as with non protein nitrogen, so even in regard to the concentration ratio the move from Group III to Group IV represents the breaking point of renal function.

TABLE 21—COMPARISON OF THE CONCENTRATION RATIO  $\frac{\text{CREATININE (URINE)}}{\text{CREATININE (PLASMA)}}$  OF THE DIFFERENT GROUPS BY QUANTILES

	No.	25 per cent	50 per cent	75 per cent	Max
Normal	15	47	116	180	4.5
Abnormal kidney					
I	15	37	67	131	305
II	15	90	50	108	245
III	5	7	44	54	125
IV	5	6	13	21	III
V	5			15	45

Finally we once more turn to the relation between plasma creatinine and creatinine excretion. Direct relation was exemplified in Fig. 43, modification or absence of such a relation in Fig. 44, in the hyperthyroid material (Table 18) this modification had reached such a degree that only an insignificant correlation existed between plasma creatinine and excretion, a high excretion being effected

normal students the coefficient of correlation is  $+0.60 \pm 0.05$  (Table 22). Group I of the kidney material includes a number of tests giving a very high filtration, the coefficient of correlation is  $+0.18 \pm 0.08$  but this difference from the normal coefficient lacks mathematical significance. Group II consists of subjects with definite reduction in the mass of filtering renal structures but with a functional capacity more than sufficient for maintenance

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the normal coefficient and from Group I as indicated by the ratios 0.31 and 0.15 in Table 22. Functionally this indicates that with progressive anatomical destruction the facility of choice in effecting



elimination, as illustrated in Fig 44, and by the hyperthyroid material, is being lost. None of the following groups approaches this correlation, though Group III, for instance, includes our subject (*Gy*, Table 15). The coefficients for Groups III to V are of little significance and no discussion is possible.

TABLE 22 — COEFFICIENT OF CORRELATION BETWEEN PLASMA CREATININE AND CREATININE EXCRETION

Material	Coefficient of correlation probable error	D. of coeff. prob. error of diff.
Normal kidneys	$\pm 0.66 \pm 0.05$	
Abnormal kidneys		1.80
I	$\pm 0.49 \pm 0.09$	
II	$\pm 0.95 \pm 0.01$	0.15*
III	$\pm 0.64 \pm 0.12$	2.76
IV	$\pm 0.46 \pm 0.20$	0.76
V	$\pm 0.25 \pm 0.26$	0.66

\* The ratio between the difference of the coefficients for the normal and for Group II and the probable error of the difference is 6.31.

**Discussion and Summary** — It has been the aim of the authors through the analysis of some 250 determinations of the rate of glomerular filtration clinically, to distinguish the rôle played by two chief mechanisms in renal function: glomerular filtration and glomerular blood flow. After elimination of glomerular blood flow as a variable the laws of glomerular filtration have been studied. Ingestion of creatinine seems to standardize the blood flow, sometimes completely, more often to a lesser and varying degree only. Glomerular filtration is passive and physical in nature. The reader has opportunity to familiarize himself with the experiments and arguments for and against this assumption. The authors further assume that the filtration is identical in health and disease. If in health the glomerular filtrate contains as much creatinine as the plasma, there is no reason for assuming that in disease creatinine would come out less easily, since under pathological conditions glomerular permeability is increased rather than decreased, *viz.*, protein retained in health, escapes in disease. Experimental evidence supports this assumption. In Fig 43 the same expression for creatinine excretion holds for the pathological case and for the normals. Therefore, when retention is present in nephritis it is due to too little kidney mass through which filtration can take place rather than to altered laws of elimination. There is little retention of urea or creatinine when the remaining units are sufficient. As a matter of fact, the

authors have stopped cutting diets below what is needed by the body as a whole even if thereby the filtration of waste products has to take place at a higher blood concentration than when the whole kidney mass is functioning.

Given filtration as an essentially constant process with the creatinine concentration of the filtrate directly dependent on its concen-

tion in advanced renal disease reduced by anatomical destruction

elimination depend more on the rate of flow than on the plasma concentration of the substance to be eliminated. Fig. 43 illustrates this situation. It is the feature which the authors are particularly desirous of discussing.

Without ingestion of creatinine normal individuals show a high positive correlation between filtration rate and body weight. In considering this fact it is worth recalling not only that creatinine output is correlated with body weight but also that creatinine output is independent of diuresis; that compared with its plasma level the urinary creatinine is concentrated more than any other substance sufficiently investigated and finally that compared with the other commonly studied waste products creatinine is present in the plasma in minute amounts only—a characteristic shared with the sulphates. In normal individuals without creatinine ingestion it appears as if creatinine determines the rate of glomerular filtration and blood flow.

Elevation of the plasma creatinine level alone must lead to increased creatinine elimination even without any increase in the rate of filtration. Actually after ingestion of creatinine by normal

correlation between filtration rate and body weight dwindles and becomes doubtful.

Instead the authors turn their attention back to the positive correlation between plasma creatinine and creatinine excretion. In all curves originating from the zero point in Fig. 43 this correlation was unity or complete. In the group of normal individuals who had taken creatinine this correlation was less complete. The group showed considerable spread of the filtration rates. This spread was assumed to be due not so much to individual differences in kidney mass as to different degrees of opening of capillaries. For

the high values the play of yet another factor, increased velocity of blood flow, is suggested. For albuminuria, Cloetta did not find this a factor of importance, but we believe that the very high filtration-rates in hyperthyroidism suggest it. Anyhow the filtration rates in hyperthyroidism proved to have such a wide spread that the correlation between plasma creatinine and creatinine excretion disappeared. On the other hand the group of diseased kidneys with normal filtration-rate showed a positive correlation between these factors which correlation did not differ from the with a function was practically referred to *vis*,

variations in blood flow under the conditions of the test had disappeared as a factor for consideration. From purely diagnostic point of view this fact has been expressed by stating that the creatinine test shows greater regularity in its results in instances of reduced function than when function is preserved.

Thus we arrive at the question of the filtration-rate as a test for renal insufficiency. When we join in Rehberg's conclusion, that a decreasing filtration-rate offers an accurate measure of deteriorating renal function we are not fortunate enough to base our conclusion upon comparisons between filtration rates and anatomical studies of diseased kidneys. For such studies Addis and Oliver<sup>1</sup> have set a high standard. It is desirable that the problem also be attacked experimentally by graded surgical reduction of the kidney mass in suitable animals.

The authors' conclusions are based upon the comparison of filtration-rate with the complete clinical picture of the patients studied supplemented by older standardized methods for testing renal function. Their only observations so far warranting a guarded interpretation of reduced filtration-rates are set down in the discussion of Table 75, in Chapter XXX.

The important factor in the discussion so far has been variation in glomerular blood flow. Comparing filtration-rate with some other features of renal activity the authors are led to a tentative discussion of tubular activity. Even where the filtration-rate was fully normal their group of pathological kidneys showed a markedly lower concentration ratio between urinary and plasma creatinine than the normal group and this ratio declined gradually, parallel with the drop in filtration rate, until the latter fell below 20 cc per minute, at which point a sharp further decline in concentration ratio occurred. This point may be considered as the point where renal function seriously breaks down as further shown by the behavior of the non protein creatinine ingestion and of products. Below this point there is a

The level of the non protein nitrogen in all the instances in which the renal function is above the breaking point deserves special consideration. Against the assumption of the authors that glomerular filtration takes place in the same manner in health and in disease the fact calls for discussion that the non protein nitrogen

with reduced function showing no greater elevation than the first. Some other mechanism than mechanical retention through reduction of glomerular surface must be operative to cause this elevation. The elevation consists chiefly of urea and the authors offer the

plasma level

If this interpretation is worthy of consideration, an inquiry may be made about phenomena that may be interpreted as evidence

in his Mellon lecture<sup>6</sup> brought out the fact that during normal pregnancy urea is present in the blood in much lower concentration than normally. The observation has been confirmed by most investigators. Among others Judson & Smith<sup>7</sup> working with one of the authors in Johns laboratory observed values as low as 12 mg non protein nitrogen per 100 cc plasma during the last months of normal pregnancy and values of 14 mg were reported by Hill<sup>8</sup> while Harding and collaborators<sup>9</sup> on whole blood found the difference barely distinguishable. Positive nitrogen balance with low urea production competes with the assumption of decreased backdiffusion as explanation of this interesting phenomenon. The latter assumption might be coupled with another one that of decreased tubular reabsorption as explanation of the transient renal glycosuria not uncommonly present during pregnancy.

#### ADDENDA

One of the authors (G. M.) carried on a series of experiments on

dogs. Blood flow was measured by the thermo-stromuhr method of Rein<sup>10</sup> since it permits observations to be made without the

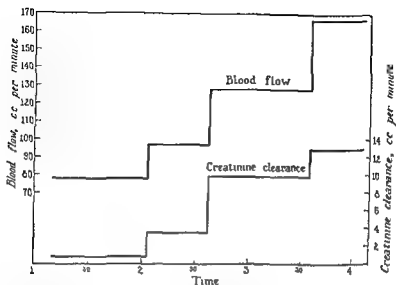


FIG 47—Parallelism between creatinine clearance and blood flow. The changes are typical for the first day of observation. (Medes and Herrick *Proc Soc Exper Biol and Med*)

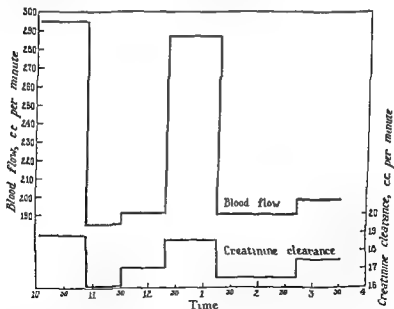


FIG 48—Parallelism between creatinine clearance and blood flow. The second day of an experiment. The increase between 12 00 and 1 00 follows a period of exercise. (Medes and Herrick *Proc Soc Exper Biol and Med*)



and observations were commenced. Glomerular filtration was measured by Rehberg's method  $1\frac{1}{2}$  to 2 gm of creatinine having been injected intravenously about one hour previously. All urine was obtained by catheter the bladder washed repeatedly with physiological salt solution and creatinine determined in the combined urine and washings.

Medes and Herrick found that where fluctuations were small

was no direct proportionality though in all cases a general parallelism existed between these two factors. Table 23 and Figs 47 and 48 give some of their findings.

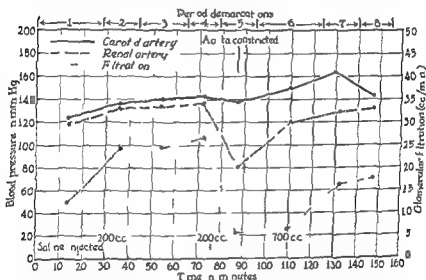


FIG. 49. Simultaneous measurements of carotid blood pressure, renal blood pressure and creatinine clearance with the blood flow to the kidneys unrestricted and restricted. (Am J Physiol 107 2:3 1933)

**Blood pressure**—Medes and Bellis<sup>24</sup> conducted simultaneous measurements of blood pressure and glomerular filtration in 2 dogs each over a period of several hours. The blood pressure was measured simultaneously from the carotid and renal arteries while a loose ligature around the aorta just above the branching of the renal arteries allowed constriction of the artery at intervals during the experiment with consequent lowering of renal blood pressure. Urine was obtained from the cannulated ureter of the opposite side and blood for creatinine estimation from the femoral artery.

The authors found that the blood pressure in the unstricted renal artery was invariably lower than that in the carotid the difference averaging about 14 mm Hg. Here again was observed a general parallelism between the two processes studied though not a strict proportionality. The authors called attention to the immediate response of the kidney to variations of pressure and pointed out that this delicate adjustment supports the hypothesis that creatinine clearance is accomplished by filtration as Rehberg postulates rather than by tubular secretion.

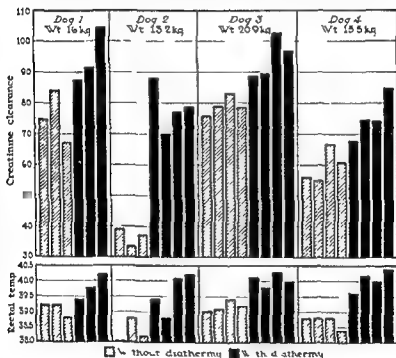


FIG. 50. Creatinine clearances of dogs before and during diathermy showing increased filtrations during elevated rectal temperatures.

**Body Temperature**—Grant and Meles<sup>13</sup> studied the relation between glomerular filtration and body temperature in a series of dogs before and during diathermy and compared these results with the changes in creatinine clearance-rates in patients with fever and after re-elevation of body temperature with fevers marked. In one instance, for example, three tests with diathermy



were made on one dog, with increases in rectal temperature of  $0.3^{\circ}$ ,  $0.7^{\circ}$  and  $1.1^{\circ}$  C respectively, while the corresponding filtrations increased 8.8, 13.1 and 25.6 cc per minute. Fig. 50 gives the results obtained in 29 tests with 4 dogs.

**Body Weight**—Grunt and Medes estimated the glomerular filtration per kilo body weight of the dogs used in their experiments and found a value of 3.9 cc per minute. The rectal temperatures of their dogs averaged  $38.8^{\circ}$  C (range,  $38^{\circ}$  to  $39.4^{\circ}$  C). They compared this filtration value with the corresponding value found in patients with fevers of infectious origin (average temperature  $38.7^{\circ}$  C range  $37.8^{\circ}$  to  $40.5^{\circ}$  C). The glomerular filtration rates of the non nephritic patients in this series averaged 3.2 cc per kilo per minute. The corresponding clearances in Medes and Herrick's series of 25 tests on 7 unilaterally nephrectomized dogs averaged 3.2 cc per kg body weight.

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CHAPTER XVI  
RENAL INSUFFICIENCY  
By FRANZ VOLHARD, M D

**Introduction** — There are few departments of internal medicine in which there has occurred such a change in our viewpoint during the last twenty years alone with such a deepening of our knowledge, incomplete though it still is, as in the field of kidney diseases. The progress proceeds, as in many other departments of medicine, from a change in perspective. The descriptive consideration of pathological anatomy, which was dominated overwhelmingly by Virchow, has become a dead issue. Two new lines of thought have developed. First, the question of the cause of the morphological changes, that is, the disease producing process, its pathogenesis. This involves consideration not only of the static factor of the anatomical and histological picture, but also of the dynamic factor

this new viewpoint has become dominant.

The first of these two more recent considerations, that of the pathogenesis of the pathological lesion, has aided the understanding of the various kinds of kidney diseases and has provided the foundation of their newer classification. The second, the functional consideration, culminates in the problem of renal insufficiency and

the labyrinth of the pathological physiology and symptomatology of renal diseases and provides fundamental orientation for understanding their general problems, as well as for exercising judgment in special cases.

The conception of renal insufficiency is still young. It was first formulated by Baron von Kórány,<sup>1</sup> at the beginning of this

a consequent tendency for increase in the osmotic pressure of the blood. He looked upon the function of the kidney as the maintenance of this pressure at constant level. His methods of testing

serum proteins

**Physico-chemical Tests of Renal Insufficiency**—The most important results of von Korányi's work are the establishment (1) that in renal insufficiency the variability of the secretion of urine is lost (2) that the molecular concentration of the urine as measured by the freezing point test (cryoscopy) diminishes and approaches that of the blood and finally (3) that the molecular concentration of the blood rises by accumulation of non-electrolytes (as measured by conductivity tests). von Korányi also saw that accumulation of electrolytes could be compensated for by retention of water (as measured by the refractometric test). The practical value of this doctrine was meager since it was built up through a study of edematous patients and the great importance of extrarenal factors in the origin of edema and in the composition of the urine was still unknown to Baron von Korányi.

Further progress followed along two lines: (1) Through chemical studies of the retention of nitrogenous waste products a field opened up by Strauss; (2) through studies in the ability of the kidney to vary the composition of the urine—by forcing the kidney and establishing the maximum capacity by the concentration and dilution test. The author has employed this test systematically for more than twenty-five years. In it the simple determination of specific gravity has been substituted for the determination of

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the water balance during twenty-four hours or following the ingestion of only 600 to 750 cc of water. In the author's test the kidney is forced to its maximum activity both as to dilution through the ingestion of 1500 cc of water and as to concentration through dry diet continued long enough to ascertain maximum concentration. The objection that his requirement of 1500 cc of water is unnatural is untenable. Maximal activity is always unnatural.

The author has confirmed the important statement of von Korányi that the concentration of the urine now measured by its specific gravity approaches in renal insufficiency the specific gravity of the deproteinized blood. He found this specific gravity to be about 1010 and called the fixation of the specific gravity of the urine at the level of that of the blood isostenuria. In agreement with von Korányi's terms hypersthenuria and hyposthenuria one could also introduce the term asthenuria indicating absolute loss of concentrating ability.

Along with loss of concentrating power the ability of the kidney to excrete a urine of large volume and low specific gravity also disappears. The author is not sure whether this loss of diluting power is a renal factor or whether it is dependent upon the high degree of retention of solid substances in the blood. In other words if it were possible to reduce the urinary constituents retained in the blood to a normal level by some other method might not the kidney be able to put out a dilute urine?

The systematic application of these principles to the study of the functional capacity of the kidney has rendered the greatest service in the understanding of renal diseases and their symptoms and in their classification and separation into stages and clinical

for testing kidney function have been brought forward. Individual foreign or naturally occurring substances have been determined quantitatively in the urine and their elimination compared with the output of a normal kidney during the same period. The observation that many edematous patients whose salt elimination is greatly diminished present a normal excretion of the nitrogenous urinary constituents was found to be functions of

many years different renal syndromes have been designated as azotemic (nitrogen retaining) and chloremic (chloride retaining).

It must be recalled in consideration of the first of these two groups the azotemic even in those cases in which nitrogen retention is

blood. When complete azotemia is present the chloride content of the urine will still be many times as great as that of the nitrogen in proportion to its higher concentration in the plasma. When chlorides are present to the amount of 600 mg per 100 cc of blood is 50 mg per 100 cc of urine to the amount of 100 mg per 100 cc of urine.

In the second group of patients with poor salt and good nitrogen elimination the so-called chloremic type the author was able to demonstrate that the impairment in this case does not lie in the kidney but in the periphery. It consists not in a decreased permeability of the renal elements but in an increased permeability of the peripheral capillaries. Such an insufficiency may therefore

the spongy subcutaneous tissue. The balance value because they do not differentiate between renal and extrarenal factors influencing rate of output and there is scarcely one method free from such sources of error. For example in the urea-concentration test introduced by Maclean and de Wesselow a kidney is considered impaired if 2 per cent concentration of urinary urea is not reached two hours after ingestion of 15 gm. of urea. However a polyuria induced by mobilization and elimination of edematous fluid may simulate impaired renal function.

**Tests With Dyes**—Least disturbed by extrarenal factors are perhaps the dye tests the indigo-carmin test of Voelcker and the phenolsulphonaphthalein test introduced by Rowntree and Graghts. But it appears for example that excretion of indigo-carmin by one healthy kidney may be severely impaired by some reflex action or toxic substance from the diseased opposite kidney and may be found normal after surgical removal of the diseased organ.

The phenolsulphonaphthalein test particularly popular in the United States is influenced by cardiac decompensation. Slight impairment of the renal function is difficult to judge with certainty. Researches of Marshall and Vickers as well as of Schlager and his school have even demonstrated the surprising fact that the dye-stuffs themselves pass from the blood into the tissues before they make their way into the urine so that no conclusion may be drawn as to the amount circulating in the blood and its proportional delivery to the kidneys. These observations seem to offer an argument against the idea so widespread that in the glomeruli simply a protein free filtrate is produced.

**Tests Based on the Excretion of Nitrogenous Waste Products**—Among the chemical methods which have made it possible to demonstrate the retention of metabolites the determination of the non-protein nitrogen first extensively used by Strauss<sup>2</sup> has well retained its place. The same holds true for the convenient though less accurate hypotomate method for urea. Numerous factors besides true kidney disease influence the level of the blood urea and the non-protein nitrogen such as cardiac decompensation probably through the slowing of the renal circulation and oliguria fever in fections surgical interventions acting by overdestruction of body protein. After enormous losses of water and salt by vomiting or diarrhea (cholera paratyphoid) we have observed values for the non-protein nitrogen as high as 200 to 300 mg. per 100 cc. values otherwise found only in true uremia.

No complete parallelism exists between the height of the blood urea and the degree of kidney insufficiency. For in tumor with

moderately advanced kidney insufficiency the level of the blood urea though elevated will vary with the protein intake a high intake will raise the level and a low reduce it more than would normally be the case. A kidney with impaired function may maintain the body for a long time in nitrogen equilibrium though by means of an elevated blood urea level. With this knowledge we reach the important rule that urea excretion depends upon the urea concentration in the blood—in contradistinction to what holds for the excretion of dyes and probably also for chlorides.

Ambard<sup>1</sup> attempted to devise for urea and later for other substances also a mathematical expression for the relationship between concentration in the blood and excretion. The pith of Ambard's rule is: The ratio of the concentration of urea in the blood to the square root of the urea output in twenty four hours = constant and in the normal individuals equals 0.07. It may be written  $\frac{U_r}{\sqrt{D}} = k = 0.07$  where  $U_r$  stands for grams of urea in 1000 cc of blood and  $D$  represents grams of urea excreted per twenty four hours.

What is the meaning of this constant? If the relationship  $\frac{U_r}{\sqrt{D}}$  is constant then for every case we can calculate the corrected blood urea value  $U_{r_x}$  which would be needed to maintain the normal excretion of urea  $D_n$ .

$$\text{Since } \frac{U_r}{\sqrt{D}} = \frac{U_{r_x}}{\sqrt{D_n}} = k$$

$$\text{then } U_{r_x} = k \sqrt{D_n}$$

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four  
 $U_{r_x}$

the constant  $\frac{U_r}{\sqrt{D}}$  by 5

The use of this may be illustrated with the following examples. If a subject has a blood urea value expressed in grams per 1000 cc of 0.28 and an output of 16 gm urea per twenty four hours we may show that his output corresponds to an excretion of 2.5 gm in twenty four hours with a normal blood urea value of 0.35 gm

i.e. since  $\frac{0.28}{\sqrt{16}} = \frac{U_{r_x}}{\sqrt{25}}$   $U_{r_x} = 0.35$  gm. But if his output with a blood urea value of 0.40 gm should amount to only 16 gm per twenty four hours then  $\frac{0.40}{\sqrt{16}} = \frac{U_{r_x}}{\sqrt{25}}$  and  $U_{r_x} = 0.50$  gm which is to say in order to excrete a normal amount of urea his blood urea would have to be at the level of 0.50 gm per liter of blood or 50 mg

per 100 cc. Again with a urea value of 0.60 gm. and a urea output of only 16 gm. per twenty four hours  $Ur_x$  would equal 0.75, that is, it would have to be 75 mg. per 100 cc., in order to produce a normal output of 25 gm. urea in twenty four hours.

If with this same blood urea level of 0.60 gm. per liter his excretion fell to 9 gm. per twenty four hours Ambard's constant would be  $\frac{0.60}{\sqrt{9}} = 0.20$  and the blood urea value needed for a nor-

mal excretion would be  $\frac{0.60}{\sqrt{9}} \times \sqrt{25} = 1.00$  gm. per liter, or 100 mg. per 100 cc. Thus by multiplication of Ambard's constant by 5 in any given case a clear picture of the degree and significance of the existing azotemia (nitrogen retention) can be obtained.

Ambard also used the constant (k) to compute the amount of functioning kidney in pathological cases. He stated that the constant of a pathological kidney is related to that of the normal one inversely as the square roots of their functioning masses. That is,  $k = \frac{a}{b}$  where  $a$  is a constant of 0.11 and  $b$  is the normal con-

In Ambard's work we had therefore won a real measure of kidney insufficiency, i. e. of the loss of kidney parenchyma in percentage, presuming that the relation given by Ambard is really a constant. The author cannot here enter into a criticism of Ambard's constant nor of the various modifications of it. He can only mention the excellent experiments of Addis and Drury and of Van Slyke and his co-workers who have evolved a somewhat different relationship between the blood urea values and the urea output. Addis and Drury and others have found that the rate of urea excretion is proportional simply to the concentration of urea in the blood and not to the square of the concentration as Ambard believed. Van Slyke and co-workers whose method described elsewhere in detail (p. 210) probably offers at present the best substitute for Ambard's added important new modifications. But it must be remembered that all chemical methods including Ambard's are tests merely for separate physiological processes and cannot reveal the functional capacity of the organ as a whole.

**Concentration and Dilution Tests of Volhard.**—The one method which gives an estimate of the total functional capacity of the kidney seems to the author to be the simple dilution and concentration test because in addition to offering a measure of capacity, it also reveals the manner of working of the insufficient kidney. With the dilution test we determine the maximum activity of one chief constituent of the kidney, the glomeruli, and with the concentration test we measure the maximum capacity of the other chief



constituent the tubules. Normally these structures differentiated for different functions are grossly independent of each other that is to say with normal tubular activity large amounts of solids might be excreted with small loss of water while with diminished concentrating power more water must be used for the elimination of the same amount of solids. An interdependence replaces the former independence. In such a case the concentration test tells us how far tubular function—concentration—is impaired the dilution test tells us of how great a polyuria the kidney is capable that is how far polyuria can compensate for loss of concentrating power.

**The Insufficient Kidney. Pathological Physiology.**—It is a great mistake to believe that the known polyuria of contracted kidneys denotes healthy capacity for secretion of water. Given an individual with a polyuria of 4 liters in twenty four hours these 4 liters may represent his total capacity to excrete water whereas the normal healthy kidney is able to put out 12 to 24 liters in the same time or 500 to 1000 cc in one-half hour.

That this compensatory polyuria has nothing to do with hypertension is unquestionable. It is quite independent of blood pressure. Also it is not the result of a primary polydipsia. It is a compulsory polyuria a *wang* polyuria which continues during the concentration test with dry foods mobilizing tissue fluids so that body weight may decrease by several kilos until progressive loss of water forces us to give up the concentration test and let the thirsty tissues drink. If the demands for excretion of solids are decreased through restricting the salt and nitrogen intake the compulsory polyuria disappears thereby revealing its compensatory character.

This picture of renal insufficiency going on from hyposthenuria with compensatory polyuria to isosthenuria with pseudo-normal uria and eventually oliguria is the same whether the result of nephritis and sclerosis and/or loss of excretive degeneration of the kidney. It is of theoretical and practical importance that the same picture is produced if the tubules are injured by pressure for example by retention of urine in the bladder due to prostatic hypertrophy or phimosis detrusor paresis etc. In these cases in which the urine is usually free from albumin and nothing points to a kidney disease the patient complains of an unexplained thirst with dry mucous membranes hoarse voice bad taste in the mouth and loss of appetite. The symptoms of renal insufficiency are often overshadowed by stomach complaints. The glomeruli remain well preserved for a long time the polyuria is pronounced and may after sudden release of the retention become very abundant and rich in degree dangerous to life. With proper handling the concentration power may return to normal. The necessity of emptying the distended bladder very gradually is not sufficiently appreciated without such precaution anuria might develop and death follow.

What is the significance of the phenomenon of isosthenuria? Is it an expression of the function of the diseased kidney elements an osmotic asthenia of the diseased kidney, as von Kórányi believed? This appears improbable, because if in animal experiments the total kidney mass is reduced to one-fourth through single nephrectomy and partial resection of the remaining kidney, as has been done by Bradford and Allen isosthenuria will result. In the author's experiments the same results followed upon single nephrectomy and ligation of two out of three of the branches of the artery to the remaining kidney (Mark). He therefore looks upon what happens in renal insufficiency as the diuresis of a quantitatively reduced kidney that is it is not the diuresis of the diseased structures, but of the still healthy elements provided their number has been reduced below a certain limit.

**Histology**—The histological picture of kidney insufficiency, whether produced through subacute or severe chronic nephritis

whether the patient died from renal insufficiency or not. If so, the kidney resembles an indurated lung with vicious emphysema. Islands of dilated tubules appear like air filled cysts in a sea of

beand up with capacity for storage, condensation and absorption of urinary constituents in the highly developed structures of the tubules. The cubical shape and abundant protoplasm of the tubular epithelium are important characteristics. If this epithelium

deformation of the epithelium we conceive to be a condition of exhaustion. The cells always at work are not given time for recovery and rebuilding of the protoplasm while normally intervals of work and rest alternate and changes of shift exist between resting and working periods. With the structural change goes an alteration in physico-chemical qualities. The normal epithelium with its abundance of protoplasm acts as a high wall and is able to preserve an osmotic pressure within the lumen widely different from that outside. The endothelial-shaped cells do not possess this power. An equalizing of the osmotic pressure takes place but without equalization of the partial concentrations. A urine isotonic with the blood results.

**Other Urinary Changes**—Another peculiarity of the urine in renal insufficiency so deserving of attention is its pale watery appearance or lack of typical urinary color. As shown by the author's co-worker Becher<sup>2</sup> this paleness is due not to retention of the urochrome the plasma too being paler than normal plasma but to a failure on the part of the kidney to oxidize the colorless urochromogen. That unoxidized chromogen is present in the pale urine was demonstrated by Becher by shaking the urine with kaolin or by exposing it to ultra violet light normal urinary color develops. This simple procedure may well be included among the tests for renal insufficiency.

How can we estimate the prognosis in renal insufficiency? Here also the investigations of Becher have made important contribution. He found that the degree of urea retention in the blood does not give a correct indication of the danger. One may even say that the accumulation of urea in the blood is not dangerous as the blood urea concentration may be elevated even more by ingestion of urea without risk. Becher was able to show that the symptoms of true uremia parallel the accumulation of products of intestinal putrefaction as phenol phenol derivatives paracresol and aromatic oxyacids in the blood. A discussion of the part played by the accumulation of these substances in the development of uremic symptoms and the modification of the xanthoprotein test which Becher devised for them are given in Chapter XXXIX on Uremia.

**Value of the Conception of Renal Insufficiency**—The more accurate knowledge of renal insufficiency is not only of practical

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acute course if the disease passes directly from the acute stage into a stage of insufficiency of a subchronic course if this stage is reached in a few years and of a chronic course when there are many years or decades before insufficiency develops

exception to be consequences of renal insufficiency. Questioning whether each phenomenon individually occurs only with or also without renal insufficiency the author has come to the surprising conclusion that neither edema nor hypertension nor retinitis nor eclamptic uremia can be considered the result of kidney insufficiency. Thus the way becomes free for the investigation of the pathogenesis

of these important and interesting effects of kidney disease, each one of which presents a problem of greatest complexity.

**Summary.**—Kidney insufficiency is a quantitative problem; it results from a reduction in the number of functioning renal units, a reduction which ultimately brings about a qualitative change in its manner of working, in that it is forced to work continuously at maximum capacity.

This is shown by a decrease in concentrating ability, hyposthenuria, with a compensatory *Zwangs-polyuria* advancing to a total loss of concentrating ability, isosthenuria. The isosthenuric urine is of constant quality and concentration, produced as it is by a kidney characterized by an inadequate number of renal elements and working night and day.

The total concentration of this urine equals that of the deproteinized blood and is represented by the specific gravity of 1010.

The partial concentrations in urine and blood may be quite different.

The total concentration of blood and urine becomes the same because the normally cubic tubular epithelium with abundant protoplasm becomes transformed through exhaustion to thin membranes.

The criterion of the degree of kidney insufficiency is the concentration test

The criterion of the capacity for compensatory polyuria (the prognosis) is the dilution test

The criterion for judging the danger to life, the xanthoprotein test

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How do we estimate the prognosis in renal insufficiency? Here

of urea concentration may be elevated even more by ingestion of urea without risk. Becher was able to show that the symptoms of true uremia parallel the accumulation of products of intestinal putrefaction as phenol phenol derivatives paracresol and aromatic oxyacids in the blood. A discussion of the part played by the accumulation of these substances in the development of uremic symptoms and the modification of the xanthoprotein test which Becher devised for them are given in Chapter XXXIX on Uremia.

**Value of the Conception of Renal Insufficiency**—The more accurate knowledge of renal insufficiency is not only of practical but also of theoretical significance. It is of practical importance in that we are better able to separate the individual case into stage and clinical course. Thus it has become practical in diffuse glomerular

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a stage of insufficiency of a subchronic course if this stage is reached in a few years and of a chronic course when there are many years or decades before insufficiency develops.

The theoretical significance is as follows: Formerly all the manifestations of kidney diseases such as dropsy increased blood pressure retinitis albuminurica and uremia were considered without exception to be consequences of renal insufficiency. Questioning whether each phenomenon individually occurs only with or also without renal insufficiency the author has come to the surprising conclusion that neither edema nor hypertension nor retinitis nor eclamptic uremia can be considered the result of kidney insufficiency. Thus the way becomes free for the investigation of the pathogenesis



## CHAPTER XVII

### BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O. BURR, PH.D. AND GRACE MEDES, PH.D.

#### DIETARY FACTORS IN FORMATION OF URINARY CALCULI

JOLI in a review of etiological factors in stone formation states that there is no very conclusive evidence that race or heredity is important. A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine. Beyond this climate seems to be relatively unimportant. In regard to geographical distribution he concludes. All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India, Mesopotamia and South China) are districts where

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out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time. In a later summary of their work Mendel<sup>23</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A\* and stated that when it is recalled that phosphatic calculi deposited in neutral or alkaline urine which in turn frequently owes its reaction to bacterial decomposition are found extensively among peoples living example in the tropics and Far East on diets quite unlike the regime of most Americans and European calculi to dietary factors is at once probable

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It is of interest to determine whether the degree of stone formation is related to the vitamin A content of the diet.

Jackson<sup>19,20</sup> reviewed the effects of a deficiency of the fat-soluble vitamins on the urinary tract. Davis and Outhouse<sup>6</sup> found a cloudy swelling of the parenchyma in the collecting tubules, but there were no visible calculi. Mori<sup>21</sup> did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson<sup>19</sup> observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Iijimaki<sup>9</sup> and Sasaki<sup>17</sup> found that concretions appeared sooner in rats on a diet deficient in vitamin A than in the controls. In the controls, calculi were formed in 10 to 15 days, while in the deficient rats they were formed in 5 to 7 days. In 6 rats stone in the bladder (shown by roentgen ray) disappeared after the animals had been placed on a diet rich in vitamin A.

McCarrison<sup>22,23</sup> has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamins. He believes that in the absence of fat-soluble vitamins certain cereals predispose rats to the formation of vesicle calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 14.6 per cent developed stones, usually of the  $MgNH_4PO_4$  type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the  $CaCO_3$  and  $Ca(OH)_2$  type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.0% drop of radiostoleum sufficed to cause a great decrease in the number of calculi. Experimental  $CaCO_3$  stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk, 3 ounces per rat daily, to a diet capable of causing urolithiasis in 40 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these



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**Vitamin Deficiency of Diet**—A considerable amount of experimental evidence has accumulated in lower animals which begins with the report of studies of rats. 81 cases of calculi were discovered. They pointed out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time. In a later summary of their work Mendel<sup>2</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A\* and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine which in turn frequently owes its reaction to bacterial decomposition are found extensively among peoples living for example in the tropics and Far East on diets quite unlike the mixed regime of most Americans and Europeans the possible relation of the calculi to dietary factors is at once prominently suggested."

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats, subsequent work has not always supported such conclusions. Probably this is due to lack in uniformity of diets and of animals. Different workers report the finding of calculi in 20 to 80 per cent of their animals, indicating a large variability in the animals themselves. Furthermore, it has been found that changes in diet, other than vitamin A content, alter the degree of stone formation.

Jackson<sup>11</sup> reviewed the effects of a deficiency of the fat-soluble vitamins on the urinary tract. Davis and Outhouse<sup>4</sup> found a cloudy swelling of the parenchyma in the collecting tubules, but there were no visible calculi. Morr<sup>12</sup> did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson<sup>11</sup> observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Iijunaki<sup>13</sup> and Suki<sup>14</sup> found that concretions appeared sooner in rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In 6 rats stone in the bladder (shown by roentgen ray) disappeared after the animals had been placed on a diet rich in vitamin A.

McArris and McArris<sup>15</sup> has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that in the absence of fat-soluble vitamins certain cereals predispose rats to the formation of vesical calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 14.6 per cent developed stones, usually of the  $MgNH_4PO_4$  type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the  $CaCO_3$  and  $Ca(OH)_2$  type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.06 drop of radiostoleum sufficed to cause a great decrease in the number of calculi. Experimental  $CaCO_3$  stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk, 3 ounces per rat daily, to a diet capable of causing urolithiasis in 70 per cent of young rats, completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

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**Vitamin Deficiency of Diet.** A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet. This begins with the report of Osborne and Mendel<sup>23</sup> that in 85 necropsies of rats 81 cases of calculi were discovered. They pointed out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time. In a later summary of their work Mendel<sup>23</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A\* and stated that when it is recalled that phosphatic calculi deposited in neutral or alkaline urine which in turn frequently owes its reaction to bacterial decomposition are found also among peoples living for example in the tropics and quite unlike the mixed regime of most Americans the possible relation of the calculi to dietary factors is suggested.

<sup>23</sup> It is noted that in 1910 only a single fat-soluble vitamin was called vitamin A and was recognized by its effect on symptoms leading to xerophthalmia. However Mellanby assigned to it a role as an antirachitic agency.

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Mcarrison<sup>25,26</sup> has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that in the absence of fat-soluble vitamins certain cereals predispose rats to the formation of vesical calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 14.6 per cent developed stones, usually of the  $MgNH_4PO_4$  type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the  $CaC_2O_4$  and  $Ca(OH)_2$  type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.06 drop of radiostoleum sufficed to cause a great decrease in the number of calculi. Experimental  $CaC_2O_4$  stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk, 3 ounce per rat daily, to a diet capable of causing uric lithiasis in 50 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

## CHAPTER XVII

### BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O. BURR, PH.D. AND GRACE MEDES, PH.D.

#### DIETARY FACTORS IN FORMATION OF URINARY CALCULI

JOLY,<sup>21</sup> in a review of etiological factors in stone formation, states that there is no very conclusive evidence that race or heredity is important. A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine. Beyond this, climate seems to be relatively unimportant. In regard to geographical distribution, he concludes: "All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India, Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule." The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary.

**Vitamin Deficiency of Diet**—A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet. This begins with the report of Osborne and Mendel,<sup>22</sup> that in 857 necropsies of rats, 81 cases of calculi were discovered. They pointed out that "in every instance where calculi developed the animals were without an adequate source of fat-soluble vitamin for some time." In a later summary of their work Mendel<sup>23</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A,\* and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living, for example, in the tropics and Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested."

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**Vitamin Deficiency of Diet**—A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet. This begins with the report of Osborne and Mendel,<sup>22</sup> that in 857 necropsies of rats, 61 cases of calculi were discovered. They pointed out that "in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time. In a later summary of their work Mendel<sup>23</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A," and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living, for example, in the tropics and Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested."

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats, subsequent work has not always supported such conclusions. Probably this is due to lack in uniformity of diets and of animals. Different workers report the finding of calculi in 20 to 50 per cent of their animals indicating a large variability in the animals themselves. Furthermore, it has been found that changes in diet other than vitamin A content alter the degree of stone formation.

Jackson<sup>12,13</sup> reviewed the effects of a deficiency of the fat soluble vitamins on the urinary tract. Davis and Outhouse<sup>14</sup> found a cloudy swelling of the parenchyma in the collecting tubules but there were no visible calculi. Mori<sup>15</sup> did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson<sup>12</sup> observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with cysts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Fujimaki<sup>16</sup> and Suki<sup>17</sup> found that concretions appeared sooner in rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In 6 rats stone in the bladder (shown by roentgen-ray) disappeared after the animals had been placed on a diet rich in vitamin A.

Mcarrison<sup>18,19</sup> has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that in the absence of fat soluble vitamins certain cereals predispose rats to the formation of vesicle calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 116 per cent developed stones, usually of the  $MgNH_4PO_4$  type. The addition of skated lard caused an increase in the incidence of stones and predisposed to the  $CaC_2O_4$  and  $Ca(OH)_2$  type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 80% drop of radiostoleum sufficed to cause a great decrease in the number of calculi. Experimental  $CaC_2O_4$  stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk, 3 ounces per rat daily, to a diet capable of causing uricthraisis in 80 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these



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**Vitamin Deficiency of Diet**—A considerable amount of experi-

out that "in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time." In a later summary of their work Mendel<sup>22</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A\* and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently *owes its reaction to bacterial decomposition*, are found extensively among peoples living, for example, in the tropics and Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested."

\* It should be remembered that in 1920 only a single fat-soluble vitamin was generally accepted. It was called vitamin A and was recognized by its effect on growth and by eye symptoms leading to xerophthalmia. However Mellanby (1918-1919) had already assigned to it a role as an antirachitic agency.

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Calcium stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk  $\frac{1}{2}$  ounce per rat daily to a diet capable of causing uric lithiasis in 70 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

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**Vitamin Deficiency of Diet**—A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet. This begins with the report of Osborne and Mendel,<sup>2</sup> that in 857 necropsies of rats 81 cases of calculi were discovered. They pointed out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time. In a later summary of their work Mendel<sup>3</sup> stated that they found many more cases among their rats on a diet deficient in vitamin A,\* and stated that 'when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living for example, in the tropics and Far East on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested.'

varied from 0 to 8 per cent (replacing Crisco) As a control diet free from vitamin A she fed a mixture of purified casein starch yeast and salts She found calculi visible to the naked eye in rats on diets very low in vitamin A (0 per cent butter) but not in rats on highly purified vitamin A free diets She believes that very early death prevented growth to macroscopic size although she does not mention having made any microscopic study Therefore, she concludes that a partial deficiency in vitamin A favors large calculi more than an absolute deficiency The possibility that the high wheat diet may have also favored stone formation is not discussed

Perlmann and Webers found phosphatic stones in the ladders of 23 per cent of rats fed on vitamin A deficient diet. Another group of 100 rats were fed limited quantities of a diet of scraps milk and carrots so that they grew to only 120 gm while the controls (20 animals) grew to 220 gm in weight 50 died within three months while 29 lived one hundred and eighty days Seven showed gravel at the end of this period The small stones consisted of urates and resembled those of human beings All normally fed rats were free from stone They conclude that vitamin A deficiency is not the only factor but is an important one Europeans have a predominance of urate stones while oxalite stones predominate among the Japanese In the case of children stones are probably due to improper feeding but in adults anatomical factors infections and disordered metabolism are the probable causes

In most of the experiments thus far mentioned both of the fat soluble vitamins A and D were low but the occurrence of calculi was ascribed by the workers to a deficiency of A only Dixon and Hoyle fed two groups of half grown rats an adequate basal ration and in addition gave them 11 and 17 mg daily of irradiated ergosterol in cacao butter Those on the smaller dose grew normally while those on the larger dose grew only slowly Autopsy showed no pathological lesions except in the urinary tract Almost without exception calcium phosphate calculi were found Since vitamin A was plentiful it was suggested that with excess of vitamin D larger amounts of calcium and phosphorus are excreted than the urine can dissolve They believe that a large excess of vitamin D in the presence of very little vitamin A would give a tendency toward calculi and in the tropics where there is much ultra violet exposure and the diet is low in vitamin A phosphatic concretions should be very common

Linn<sup>14</sup> reared rabbits on a diet deficient in the fat-soluble vitamins A and D (ground bark, casein, lard, salts, oryzanin and radish juice) He ran controls on a normal rabbit ration okara Of 43 animals on the basal ration nine for thirty five to one hundred and seven days 7 per cent in heated gall stones 17 per cent

## BIOLOGICAL FACTORS IN STONE FORMATION

nephroliths and 2 per cent both calcium ovalates and phosphates. The nephroliths contained greater frequency in the right kidney. Limited data indicate greater vitamin A deficiency in many. But only 65 per cent of the animals with calculi developed eye trouble. He believes that there are at least two factors and that calculus formation is closely related to vitamin D.

I sum<sup>22</sup> attempted to find the effects of vitamin A deficiency on the blood serum of rabbits which might account for the appearance of stones. Sodium potassium calcium magnesium cholesterol and fatty acids were determined. Those cases which developed calculi appeared all blood constituents increased calcium and cholesterol increasing most. Calculi appeared in some cases where symptoms of avitaminosis were lacking.

Abderhalden (1931) reports an unusually large number of sarcomas and urinary bladder stones in rats fed a diet of milk and rice. This diet permits the animals to reach an advanced age, but pelagra like symptoms often occur. The diet probably is not very low in vitamin A.

Pontius Carr and Doyle<sup>23</sup> report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate. When sheep have calculi the urine from their bladders is always strongly alkaline. They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates. They studied the effect of diet on the pH and ash of sheep's urine. With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent.

Easterfield and Bruce<sup>24</sup> report xanthine calculi in the kidneys of some New Zealand sheep. They attribute these stones to a deficiency of minerals in the pasturage.

**Mineral Unbalance of Diet**—In view of the present state of the literature pertaining to the experimental production of calculi only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation. The lack of vitamin A has produced calculi in a large number of experiments but it has frequently failed to do so. An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A and in some cases a high calcium diet produces stone even when vitamin A is plentiful. Cattle and sheep living on alfalfa grass and other green pasturage certainly receive an abundance of vitamin A. Nevertheless calculi frequently occur in their urinary tracts. Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of the

earthy phosphates (Hellström<sup>11</sup>) and frequently leads to the depositing of calculi with organic nuclei. Consequently the effect of diet on the pH of the urine should always be considered.

As Joly<sup>12</sup> has pointed out, calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet. Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates, yet

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shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet.

With one exception the experimental stones in rats and rabbits

to date have not thrown much light on the cause of these calculi in man.

The only experiment in which urate calculi have been reported is that of Lickmann and Weber.<sup>13</sup> It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency. This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition.

## CHEMICAL FACTORS IN STONE FORMATION

**Colloidal Precipitation**—The role of mucus or other colloidal binder in certain types of concretions has been recognized since the time of Hippocrates and Galen. A. von Heyde (1884) initiated experimental work by dissolving out the crystalline salts of urinary calculi and observing the framework, and Hemsbach<sup>14</sup> stated that this framework was unquestionably necessary for true stone formation, since otherwise urinary salts can only yield crystalline pulverulent or granular precipitates. This point of view became widely accepted, although it was recognized that certain stones of non-inflammatory origin, such as uric acid stones in the kidney and bladder and cholesterol stones in the gall bladder, might occasionally be found in which no organic binder could be demonstrated. It remained for colloidal chemistry, under the leadership

nephroliths and 2 per cent both. The nephroliths contained calcium oxalates and phosphates. Limited data indicate greater frequency in the right kidney. There were definite symptoms of vitamin A deficiency in many. But only 65 per cent of the animals with calculi developed eye trouble. He believes that there are at least two factors and that calculus formation is closely related to vitamin D.

Usuni<sup>24</sup> attempted to find the effects of vitamin A deficiency on the blood serum of rabbits which might account for the appearance of stones. Sodium, potassium, calcium, magnesium, cholesterol and fatty acids were determined. Those cases which developed xerophthalmia showed a marked increase in serum calcium. If calculi appeared all blood constituents increased, calcium and cholesterol increasing most. Calculi appeared in some cases where symptoms of vitaminosis were lacking.

Abderhalden (1931) reports an unusually large number of sarcomas and urinary bladder stones in rats fed a diet of milk and rice. This diet permits the animals to reach an advanced age but pellagra-like symptoms often occur. The diet probably is not very low in vitamin A.

Pontius, Carr and Doyle<sup>25</sup> report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate. When sheep have calculi the urine from their bladders is always strongly alkaline. They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates. They studied the effect of diet on the pH and ash of sheep's urine. With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent.

Easterfield and Bruce<sup>26</sup> report uric acid calculi in the kidneys of some New Zealand sheep. They attribute these stones to a deficiency of minerals in the pasturage.

**Mineral Unbalance of Diet**—In view of the present state of the literature pertaining to the experimental production of calculi, only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation. The lack of vitamin A has produced calculi in a large number of experiments but it has frequently failed to do so. An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A and in some cases a high calcium diet produces stone even when vitamin A is plentiful. Cattle and sheep living on alfalfa grass and other green pasturage certainly receive an abundance of vitamin A. Nevertheless calculi frequently occur in their urinary tracts. Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of the

earthy phosphates (Hellström<sup>15</sup>) and frequently leads to the depositing of calculi with organic nuclei. Consequently the effect of diet on the pH of the urine should always be considered.

As Joly<sup>16</sup> has pointed out, calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet. Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates, yet the people subsist largely on rice which is nearly purine-free. In general, calculi are common only where the diet is very monotonous and are uncommon where the diet is varied. This fact indicates that stone formation is really a deficiency disease rather than the result of an excess of stone-forming materials in the diet. However, it seems clear that the composition of the diet affects the composition of the stones (McCarrison, Van Leeuwen). Hangerman<sup>17</sup> has shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet.

With one exception, the experimental stones in rats and rabbits have been reported to be largely calcium, magnesium and ammonium phosphates, carbonates and oxalates. Since a large percentage of human stones are composed of uric acid and urates, the experiments to date have not thrown much light on the cause of these calculi in man.

The only experiment in which urate calculi have been reported is that of Erlmann and Welser.<sup>18</sup> It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency. This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition.

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comas and urinary bladder stones in rats fed a diet of milk and rice. This diet permits the animals to reach an advanced age but pellagra like symptoms often occur. The diet probably is not very low in vitamin A.

Pontius, Carr and Doyle<sup>55</sup> report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate. When sheep have calculi the urine from their bladders is always strongly alkaline. They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates. They studied the effect of diet on the pH and ash of sheeps' urine. With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent.

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**Mineral Unbalance of Diet**—In view of the present state of the literature pertaining to the experimental production of calculi only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation. The lack of vitamin A has produced calculi in a large number of experiments but it has frequently failed to do so. An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A and in some cases a high calcium diet produces stone even when vitamin A is plentiful. Cattle and sheep living on alfalfa grass and other green pasturage certainly receive an abundance of vitamin A. Nevertheless calculi frequently occur in their urinary tracts. Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of the

earthy phosphates (Hellstrom<sup>21</sup>) and frequently leads to the depositing of calculi with organic nuclei. Consequently the effect of diet on the pH of the urine should always be considered.

As Joly<sup>22</sup> has pointed out, calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet. Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates, yet the people subsist largely on rice which is nearly purine free. In general, calculi are common only where the diet is very monotonous and are uncommon where the diet is varied. This fact indicates that stone formation is really a deficiency disease rather than the

shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet.

With one exception, the experimental stones in rats and rabbits have been reported to be largely calcium, magnesium and ammonium phosphates, carbonates and oxalates. Since a large percentage of human stones are composed of uric acid and urates, the experiments to date have not thrown much light on the cause of these calculi in man.

The only experiment in which urate calculi have been reported is that of Perlmann and Weber.<sup>4</sup> It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency. This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition.

## CHEMICAL FACTORS IN STONE FORMATION

**Colloidal Precipitation.** The role of mucus or other colloidal binder in certain types of concretions has been recognized since the time of Hippocrates and Galen. A. von Heyde (1654) initiated experimental work by dissolving out the crystalline salts of urinary calculi and observing the framework. and Hemsbach<sup>23</sup> stated that this framework was unquestionably necessary for true stone formation, since otherwise urinary salts can only yield crystalline pulverulent or granular precipitates. This point of view became widely accepted although it was recognized that certain stones of non-inflammatory origin such as uric acid stones in the kidney and Heller and cholesterol stones in the gall bladder might occasionally be found in which no organic binder could be demonstrated. It remained for colloidal chemistry under the leadership

of Schade<sup>22</sup> and Aschoff<sup>1</sup> following the early experiments of Ord<sup>23</sup> to demonstrate that the same colloidal processes occur in all stone formation. Schade<sup>22</sup> postulated that the fundamental step in calculus formation is the irreversible precipitation of some hydrophilic colloid which may (Type I) remain as a pure colloid concretion or (Type II) become the matrix in which crystalloids of different origin form varying amounts of the stone or (Type III) subsequently undergo crystallization with the formation of a pure crystalloid concretion.

**Role of Urinary Colloids in Kidney Stone Formation**—Morner<sup>26</sup> investigated the colloids of normal urine and identified an albumin which he believed to be identical with serum albumin, chondroitin sulphuric acid and nucleic acid. Salkowski<sup>25</sup> isolated a non-diffusible carbohydrate containing a nitrogen complex. Various estimates have been made of the total amount of these colloids present. Lichtwitz (1914) dialyzed urine against distilled water and estimated the amount of colloids remaining undialyzed. He found an average of 0.85 gm. of colloid per liter of urine.

There is little evidence that the colloids of normal urine form the matrix of urinary calculi but rather that they act as protective colloids stabilizing the solution. Calculi of Type II are usually classified as being of inflammatory origin. Schade<sup>21</sup> classified Type I as originating without inflammation but Troltzsch<sup>28</sup> in reviewing all the known cases has showed that in all but 3 questionable instances either infection of the kidney or some pathological state was present. Moreover it seems more logical that Types I and II occur under similar conditions except that in the latter case the urine is also supersaturated with some crystalloid constituent which

date 25 cases had been reported. Troltzsch groups these calculi in three classes: (a) albuminous (including those composed of fibrin), (b) bacterial and (c) amyloid. Of the 29 cited 13 were of a 12  
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The crystalloids which may be present in urine in mixed Type II are uric acid and the urates, calcium oxalate, the phosphates of calcium, magnesium and ammonium, calcium carbonate, cystine—all substances may be present in urine in larger quantities than would be expected from their solubilities in water. For instance, the solubility of uric acid at 37°C. is as 65 parts of water to 1 part of uric acid, approximately twenty

times this amount may be excreted by a normal individual in twenty-four hours. Seidell<sup>18</sup> records the solubility of calcium oxalate

in maintaining various crystalloids in their supersaturated state has been investigated by numerous workers. Pauli and Samec<sup>19</sup> compared the solubilities of various substances in distilled water with their solubilities in blood serum and in 1.5 per cent albumin solution and gave the following figures:

TABLE 25

Solubility in gm. at 25° C. in 100 gm. solution

	H <sub>2</sub> O gm.	Serum gm.	1.5 per cent gelatin gm.
Calcium phosphate (Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> )	0.011	0.091	0.018
Calcium carbonate	0.004	0.099	0.015
Uric acid	0.040	0.057	

Joly<sup>21</sup> states that if a specimen of urine is dialyzed through a parchment membrane against a large quantity of water the crystalloids will diffuse through the membrane while the colloids will be left behind. If this solution of the urinary crystalloids is slowly

concentrating the dialysate to the volume of the original urine there was no precipitation, provided the original acidity was maintained.

**The Peptizing Action of Urea**—Another substance whose capacity to increase the solubility of other constituents of urine should be considered is urea. As the unsaturated amide of carbonic acid, urea combines with acids to form salt-like compounds, many of which are highly soluble. The nitrate and the oxalate are well known. DuRoi<sup>22</sup> identified seven other such compounds of urea with oxalic, acetic, hydrochloric, nitric and sulphuric acids, all except  $\text{UrHNO}_3$  being highly soluble. Urea also forms additional compounds with salts, probably through the residual valence of its oxygen. For instance, 1, 2, 3, 4 or more molecules of urea may unite with calcium chloride to form a series of more or less unstable hygroscopic salts. Many strains of staphylococci, the most common organisms in calcareous kidneys, are urea-splitting and hence by the formation of ammonia produce an alkaline urine in which

of Schade<sup>49</sup> and Aschoff<sup>1</sup> following the early experiments of Ord<sup>50</sup> to demonstrate that the same colloidal processes occur in all stone formation. Schade<sup>51</sup> postulated that the fundamental step in calculus formation is the irreversible precipitation of some hydrophilic colloid which may (Type I) remain as a pure colloid concretion or (Type II) become the matrix in which crystalloids of different origin form varying amounts of the stone or (Type III) subsequently undergo crystallization with the formation of a pure crystalloid concretion.

**Role of Urinary Colloids in Kidney Stone Formation**—Morner<sup>52</sup> investigated the colloids of normal urine and identified an albumin which he believed to be identical with serum albumin, chondroitin sulphuric acid and nucleic acid. Salkowski<sup>48</sup> isolated a non-diffusible carbohydrate containing a nitrogen complex. Various estimates have been made of the total amount of these colloids present. Lichtwitz (1914) dialyzed urine against distilled water and estimated the amount of colloids remaining undialyzed. He found an average of 0.85 gm. of colloid per liter of urine.

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Troltzsch =  
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date 25 cases had been reported. Troltzsch groups these calculi in three classes: (a) albuminous (including those composed of fibrin), (b) bacterial and (c) amyloid. Of the 29 cited 13 were of a, 12 of b and 4 of c. Those of a and b grade over into each other and according to him albumin or fibrin supplies the ground substance for both the bacterial and the amyloid.

The crystalloids which may be present in the concretions of mixed Type II are uric acid and the urates, calcium oxalate, the phosphates of calcium, magnesium and ammonium, calcium carbonate, cystine—all substances which may be present in urine in larger quantities than water. For instance 37° C. as 65 mg. per

times this amount may be excreted by a normal individual in twenty four hours. Seidell<sup>10</sup> records the solubility of calcium oxalate at 21° C. as 0.2 mg. per liter of a 1 per cent solution. MacCaffrey<sup>11</sup>

in maintaining various crystalloids in their supersaturated state has been investigated by numerous workers. Pauli and Samec<sup>12</sup> compared the solubilities of various substances in distilled water with their solubilities in blood serum and in 1.5 per cent albumin solution and gave the following figures:

TABLE 5

	Solubility in gm. at 20° C. in 100 gm. solution		
	H <sub>2</sub> O gm.	Serum gm.	1.5 per cent gelatin gm.
Calcium phosphate (Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> )	0.011	0.01	0.018
Calcium carbonate	0.004	0.027	0.015
Uric acid	0.040	0.057	

Joly<sup>1</sup> states that if a specimen of urine is dialyzed through a parchment membrane against a large quantity of water the crystalloids will diffuse through the membrane while the colloids will be left behind. If this solution of the urinary crystalloids is slowly evaporated down it will be found that a copious deposit forms long before the solution is concentrated to the original volume of the urine. These findings were not substantiated by Newcomb<sup>13</sup> who repeated the experiment and found that uric acid distributed itself evenly on both sides of the membrane and hence could not be attached to the urinary colloids. Moreover he found that on concentrating the dialysate to the volume of the original urine there was no precipitation provided the original acidity was maintained.

**The Peptizing Action of Urea.**—Another substance whose capacity to increase the solubility of other constituents of urine should be considered is urea. As the unsaturated amide of carbonic acid, urea combines with acids to form salt-like compounds many of which are highly soluble. The nitrate and the oxalate are well known. DuRoi<sup>14</sup> identified seven other such compounds of urea with oxalic, acetic, hydrochloric, nitric and sulphuric acids all except Ur.HNO<sub>3</sub> being highly soluble. Urea also forms additional compounds with salts probably through the residual valence of its oxygen. For instance 1, 2, 3, 4 or more molecules of urea may unite with calcium chloride to form a series of more or less unstable hygroscopic salts. Many strains of staphylococci the most common organisms in calcareous kidneys are urea-splitting and hence by the formation of ammonia produce an alkaline urine in which



the solubility of phosphates is low, and at the same time deprive the urine of urea, one of its stabilizing factors

One of the authors (G M) tested the solubility of calcium oxalate and uric acid in solutions of urea and found that urea exerts a peptizing effect, increasing the solubility of the oxalate from 0.63 mg per 100 cc of solution (in water) to 8.02 mg per 100 cc of solution (in 50 per cent urea), and producing a slight increase in solubility of uric acid

TABLE 26—SOLUBILITY OF CALCIUM OXALATE IN AQUEOUS SOLUTIONS OF UREA (100 MG OF CALCIUM OXALATE  $\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$  + UREA AND MADE UP TO 100 CC WITH WATER) (THE SOLUBILITY OF URIC ACID IS EXPRESSED IN MG PER 100 CC OF SOLUTION) TEMPERATURE  $22.6^\circ \text{C}$

Urea (gm)	0.06	0.15	0.80	3.00	16.00	50.00
Solubility $\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$	0.63	0.66	0.70	0.82	1.23	8.02

TABLE 27—SOLUBILITY OF URIC ACID IN SOLUTIONS OF UREA GRAMS OF UREA + 80 MG URIC ACID MADE UP TO 100 CC WITH  $\text{CO}_2$  FREE WATER THE SOLUBILITY OF URIC ACID IS EXPRESSED IN MG PER 100 CC OF SOLUTION TEMPERATURE  $26.2^\circ \text{C}$

Urea gm	Solubility uric acid mg	Urea gm	Solubility uric acid mg	Urea gm	Solubility uric acid mg
	4.39	6.00	9.21	16.00	8.59
0.16	4.78	8.00	9.73	18.00	7.80
4.40	5.33	10.00	11.52	20.00	7.65
2.00	6.44	12.00	10.67	80.00	7.12
4.00	6.88	14.00	9.30		

The rise in solubility of calcium oxalate in solutions of urea is continuous, indicating that there is some peptizing action but that molecular combinations are not formed. When urea is present to the extent of 3 per cent, the amount of calcium oxalate which may be held in solution is doubled. Fifteen hundred cc of urine, saturated with calcium oxalate and containing 3 per cent urea would contain 19 mg calcium oxalate an amount approximating the average daily output of a normal individual.

The increase of solubility of uric acid is insufficient to account for the amount which may be present in normal urine, since in a volume of 1500 cc containing 3 per cent urea only about 100 mg of uric acid could be dissolved, whereas 250 mg to 1 gm might be excreted. Gudzent<sup>11</sup> found the solubility of potassium urate to be 2.7002 gm per liter of solution at  $37^\circ \text{C}$  of sodium urate as 1.5043 gm and of ammonium urate as 0.7413 gm per liter, but since all the acid

phosphate buffer mixtures containing borates and found that at pH 6.4 the solubility was 0.1123 gm per liter of solution at  $37^\circ \text{C}$ , as compared with 0.0328 gm per liter at pH 5.4. At pH 7.4 the

solubility was 0.911 gm per liter and at pH 8 3.56 gm per liter. Harpuder and Erbsen<sup>17</sup> investigated the solubility of uric acid in various buffer mixtures using  $\text{Na}^+$  as the cation. They reported that at any given pH the solubility was affected by the nature of the anions composing the buffer solution. Assuming Jung's findings hold for urine, even at pH 11.4 the increased solubility due to salt formation together with the peptizing action of urea on the free acid (about 97 per cent of the total) would account for all the uric acid of normal urine provided the output of uric acid is low and the diuresis moderately large (about 1500 cc). At a pH of 7.4 the solubility would be sufficiently increased by these two factors to account for the maximum normal output (of about 1 gm).

**Physico-chemical Studies—Effect of pH**—The extensive work of Schade has given us an insight into the physico-chemical laws governing the formation of pure crystalline stones (Type III). He has showed<sup>20</sup> that from a supersaturated solution of uric acid more acid than pH 5.5 or of sodium urate more alkaline than pH 7 well-formed crystals appear but within a zone between 5.5 to 7 uric acid separates in droplets discernible only by means of the ultra-microscope. If this guttulate separation is not disturbed by too  
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crystallization become radially marked firm spherulites. Since growth in these stones is frequently continuous by the constant addition of droplets the structure of such stones is generally homogeneous throughout their entire mass and layering is frequently absent.

Uric acid undergoes this preliminary guttulate separation from pure aqueous solution but oxalates require the presence of precipitable colloids. Ord<sup>18</sup> early described radially striated balls of oxalates in gelatin solutions and Hatschek<sup>19</sup> produced them also from solutions of agar. Schade states that similar observations exist with regard to calcium carbonate.

Weiser and Gray<sup>21</sup> contend that the conditions are more complex,

shifts in the pH of the urine. Meyer (1929) investigated the

conditions under which the various deposits may be formed. He gives the following

pH	Type of calculus
About 5	Pure uric acid
6	Mixed, of pure dense uric acid, urate, oxalate and Ca phosphate
7	Ca phosphate
8-7	Hard stratified calculi, chiefly of $MgNH_4PO_4$ , Ca phosphate and $NH_4$ urate in ammoniacal urine (deposit slowly)
8	Soft free calculi, chiefly $MgNH_4PO_4$ , $CaCO_3$ , and $NH_4$ urate (deposit rapidly). Considerable amounts of $CaCO_3$ indicate highly alkaline urine

Pure crystalline stones of unmixed type also show a tendency to banding although a radial structure of the crystals is more pronounced. This banding occurs most frequently when numerous small stones are present as for instance, in multiple gall stone formation and Schade<sup>41</sup> attributes the layering to a flattening of the added droplets before crystallization due to the pressure of neighboring stones. The remarkable regularity of the bands have suggested to colloid chemists the similarity to Liesegang's rings which Liesegang produced by the precipitation of silver chromate when he allowed silver nitrate to diffuse into a gelatin gel containing dichromate. Schade's objection to this explanation was based upon his idea that precipitation of bands could not occur with such rhythmic regularity when preformed crystals offered points of resistance to diffusion. Weiser and Gray<sup>42</sup> however, reproduced the phenomenon in gelatin gels containing minute crystals of cholesterol, even when the concentration of gelatin was as low as 0.05 per cent. They conclude by their experiments that the rhythmic precipitation takes place in the mass of minute crystals and that the gelatin jelly merely serves to inhibit their growth and so to maintain a mass of fine crystals in which the diffusion and precipitation may occur.

§ *Potential* Mere supersaturation of urine with colloid capable of irreversible coagulation does not necessarily cause stone formation, the effects not only of other protective colloids but also of electrolytes must be considered. Powis<sup>43</sup> has shown that when colloids

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an extensive study of the physico-chemical laws of gall stone for-

mation have measured the effects of anions and cations and of  $H^+$  and  $OH^-$  on the  $\zeta$  potential. They showed that monovalent cations such as  $Na^+$  and  $K^+$  increase the potential when present in small amounts and decrease it to the critical zone only when present in comparatively high concentrations. The divalent ions  $Ba^{++}$ ,  $Ca^{++}$  and  $Mg^{++}$  produce a slighter initial increase and smaller amounts are required to lower the potential to the critical zone than with monovalent ions. The trivalent ion  $Al^{+++}$  produces an immediate lowering toward the zero zone in which the colloid loses its stability and flocculates. In higher concentrations of the

one another following the lyotropic series as showed by Briggs<sup>4</sup> the greater the movement velocity the smaller the  $\zeta$  potential in series  $Li^+$   $Na^+$   $K^+$   $Rb^+$   $NH_4^+$  and  $Cs^+$  lower concentra-

favorable for coagulation of any irreversibly precipitating colloid present in the urine.

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## PART III

# BRIGHT'S DISEASE AND VARIOUS OTHER PATHOLOGICAL RENAL CONDITIONS

### CHAPTER XVIII

## THE PATHOLOGY OF THE MAIN NEPHROPATHIES

By E. T. BELL, M.D.

### DEGENERATIVE NEPHROPATHIES—NEPHROSES

NEPHROSIS is generally understood to include degenerative renal lesions in contradistinction from nephritis which designates inflammatory lesions. The term nephrosis is not literally accurate.

and in many instances of nephrosis there are mild inflammatory reactions. It is also uncertain whether thickening of the glomerular capillary basement membrane is an inflammatory or a degenerative process. For practical purposes it is probably better to diagnose nephrosis when the lesion is chiefly degenerative and nephritis when it is chiefly inflammatory rather than to recognize mixed types.

Degenerative  
granular and fat

Inflammatory  
interstitial tissues; excessive accumulation of blood leukocytes in the glomerular capillaries or capsular spaces; increase in the number and size of the glomerular capillary endothelial cells; and increase in the number of cells in either the parietal or the visceral epithelial layer of Bowman's capsule.

There is some doubt as to the interpretation of changes in the capillary basement membrane. The increase in thickness of this  
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All cases of nephrosis except the lipoid group are secondary to some other disease. If the clear urine may result in uremia. Albuminuria and casts are often the only evidence of

renal injury but in special instances edema hypertension, anuria or renal insufficiency may develop

number of chemical poisons have been used to produce renal lesions. Those most frequently employed for this purpose are uranium nitrate potassium bichromate mercuric chloride and racemic tartaric acid. The lesion produced by a chemical poison is always a nephrosis never a nephritis.

In clinical experience mercuric chloride nephrosis is about the only one of the chemical group that is encountered. Persons that survive a day or longer after taking the poison develop anuria immediately or after a period of oliguria. The urine shows albumin and casts. There is a progressive rise of the blood metabolites. There is no edema except a little in the face occasionally. Hypertension develops in some instances during the period of anuria. Death occurs in uræmia. In the event of recovery all evidence of renal disease finally disappears. A chronic nephropathy does not develop.

At postmortem the kidneys are slightly swollen and very cloudy. Necrosis and disintegration of the cells of the convoluted tubules are outstanding histological features. In those that die after several days calcified epithelial cells are frequently seen some of which are detached and others still connected with the basement membrane. Newly formed epithelial cells begin to displace the necrotic ones after a few days.

**2 Nephroses Due to Bacterial Poisons**—The majority of persons suffering from severe infectious diseases and infections show albumin and casts in the urine. The infectious diseases which show albuminuria most frequently are lobar pneumonia diphtheria

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are usually somewhat enlarged and on section the cortices are always cloudy. The cells of the convoluted tubules are swollen the cytoplasm often has a more vesicular structure and it may contain hyaline granules or fat droplets. Necrosis is rarely seen but in unusually severe infections notably diphtheria necrotic tubules may be found (nephrotic nephrosis). The glomeruli appear normal in most instances but frequently especially in pneumococcal and streptococcal infections there is a distinct increase in the number and size of the capillary endothelial cells or an increase in the number



of polymorphonuclear leukocytes. Sometimes the new cells in the capillaries are chiefly endothelial, sometimes chiefly polymorphonuclear leukocytes. Inflammatory reaction of endothelial cells.

are not examples of a pure nephrosis as defined above. They are really early stages of acute glomerulonephritis. The glomerular lesions are fairly uniform and therefore cannot be interpreted as focal glomerulonephritis. Such kidneys with mild glomerulitis cannot be distinguished clinically or macroscopically from those in which inflammatory changes are absent.

**3 Nephroses Due to Jaundice** In severe obstructive jaundice albuminuria is often found. The obstruction is so frequent. There

thought that the renal injury is due to bile acids since these substances are said to increase in the blood after a short period of obstruction but to decrease after prolonged obstruction. At post mortem the degree of cloudy swelling is obscured by the jaundice. Microscopically minor degenerative changes are found in the tubules.

**Special Nephroses**—This group includes special renal diseases which correspond more closely to nephrosis than to nephritis but which cannot be regarded as purely degenerative in character.

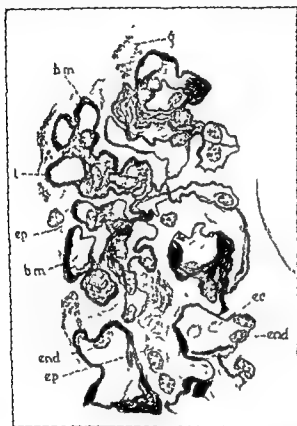
**1 The Nephrosis of Eclampsia** Eclampsia rarely develops before the fifth month of gestation. Occasionally the first symptoms appear during or after labor. The more prominent clinical features are albuminuria, hypertension, edema, convulsions, visual disturbances and headache. Apparently no single symptom is absolutely essential in establishing the diagnosis. There are a number of instances without convulsions reported in which hemorrhagic necrosis of the liver was found at postmortem.

There is a retention of water and sodium chloride in eclampsia probably dependent upon extrarenal factors. The non protein nitrogen of the blood is normal or slightly elevated. Aside from the rare cases of cortical necrosis there is very little renal insufficiency.

At postmortem the most characteristic lesions are found in the liver and kidneys. In the liver one finds on macroscopic examination irregular areas of hemorrhagic necrosis in most instances but occasionally these lesions are not found.

The kidneys are invariably swollen and on section the cortices are pale and cloudy. The tubular epithelial cells are swollen and they may contain a number of small lipid droplets. The characteristic changes are found in the glomeruli. In sections stained with hematoxylin and eosin it is noted that they are slightly enlarged and anemic. On detailed examination it is found that the glomerular capillaries are very narrow and that this narrowing is

usually due to thickening of the capillary walls rather than to increase of endothelium. In sections stained by the Mallory-Heidenhain technique it is seen that there is a very marked thickening of the capillary basement membrane (Fig. 51). The thickened



— eosin stain  
 — erythrocyte  
 — black end endothelial cell (Bell)

membrane causes narrowing of the capillary lumen. Usually there is no increase of endothelial nuclei, but in an occasional case the endothelial increase is a more prominent cause of capillary obstruction than thickening of the basement membrane. The basement membrane shows a definite thickening in every instance, but it is

more pronounced in some cases than in others. Narrowing of the capillaries increases the resistance to the flow of blood through the kidneys and is probably the immediate cause of hypertension.

In rare instances widespread cortical necroses are found in eclampsia.

It is obvious that eclamptic kidneys with a definite increase of glomerular endothelium are not instances of pure nephrosis and one must interpret thickening of the basement membrane as a degenerative process in order to hold any eclamptic kidney in the group of nephroses.

When a patient with chronic glomerulonephritis becomes pregnant there is usually an increase of the intensity of the nephritic symptoms viz albuminuria, edema, hypertension, etc. These cases of nephritis are apt to be confused with eclampsia unless the patient has been studied prior to the pregnancy or unless a definite renal insufficiency is present.

The attack of eclampsia may leave some permanent damage in the kidneys. In 1 of the author's cases in which the kidneys were studied seven years after eclampsia there were numerous hyaline glomeruli with atrophic tubules and other glomeruli with large fibrous areas in them.

**2 The Amyloid Kidney**—Amyloid disease of the kidneys is usually associated with amyloidosis of other organs but rarely it occurs independently. Clinically the renal lesion is usually overshadowed by the major illness but in rare instances the picture is predominantly one of renal disease. The most frequent cause is tuberculosis with suppuration viz pulmonary tuberculosis with cavities and tuberculosis of the spine but a large variety of chronic suppurative processes may cause amyloidosis. Occasionally no cause of the amyloid deposit can be found.

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of the basement membrane. The blood pressure becomes high. Amyloid nephrosis is a picture

of chronic uremia develops. The blood pressure may become

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Amyloid is deposited chiefly in the glomeruli (fig. 52). It accumulates in the capillaries on the inner surface of the basement membrane never on its external surface. When the deposit is small it is often possible to demonstrate the basement membrane

external to the amyloid, but sometimes the first deposit obliterates the membrane and when the capillaries are filled the membrane cannot be distinguished. Any endothelial nuclei which may be present are pushed toward the lumen and enclosed in the amyloid mass. The capillaries may remain permeable to the blood even after the glomerulus is greatly enlarged from amyloid infiltration, but finally, they are obstructed completely and disuse atrophy of the tubule sets in. The deposit of amyloid in the muscular coats of the small arteries and arterioles also tends to cut off the blood supply of the glomeruli. Another factor in destruction of the



FIG. 52 — Amyloid nephrosis. Glomerulus showing a majority of its capillaries filled with amyloid. Photomicrograph.

tubules = plugging of their lumens with numerous large casts and occasionally also the deposit of amyloid under their basement membranes. Amyloid is commonly deposited also in the walls of the vasa recta. As a result chiefly of glomerular obstruction and casts renal insufficiency develops. Amyloid kidneys with uremia may be contracted or large. Hyaline granular degeneration of the tubules is frequent in amyloid disease.

begins

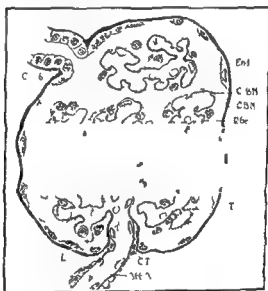
Lipoid nephrosis will be discussed under Glomerulonephritis

## GLOMERULONEPHRITIS

Glomerulonephritis is defined broadly as a disease in which there are inflammatory changes of any kind in the glomeruli. The evidences of an inflammatory reaction are swelling and proliferation of the capillary endothelium, excessive accumulation of blood leukocytes in the glomerular capillaries and formation of intra-capillary fibers. The result of the various inflammatory reactions

it is of secondary importance

We distinguish a diffuse type in which practically all the glomeruli are involved and a focal type in which only a part of them are affected



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**Diffuse Glomerulonephritis** —In order to give a clear presentation

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basement membrane, which is covered externally by the glomerular epithelium and lined internally by endothelial cells. There are relatively few endothelial nuclei. The great majority of the nuclei in a normal glomerular tuft belong to the epithelial cells. The endothelial cells apparently do not form a continuous layer. The capillary basement membrane is continuous with the capsular basement membrane which is an extension of the basement membrane of the convoluted tubule. The proper staining of the capillary basement membrane is essential in the study of the finer histology of glomerular lesions.

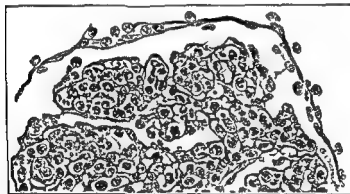


FIG. III.—Acute exudative glomerulonephritis, non-clinical type. From a case of lobar pneumonia. Note large number of polymorphonuclear leukocytes within the capillaries. Drawing.

1. **The Non-clinical Type**—The non-clinical type is found frequently if one makes a routine microscopic study of kidneys from persons dead of infectious processes. The clinical picture is that of a nephrosis secondary to bacterial infection. The characteristic clinical findings of glomerulonephritis, viz., edema, hypertension, etc., are absent. In the author's experience, puerperal sepsis, lobar pneumonia and streptococcic bacteremia most frequently give rise to this lesion.

At postmortem the kidneys show a marked degree of cloudy swelling. The tubular epithelium is swollen and may contain hyaline-granular and fat droplets. The glomeruli all show an increase of nuclei. On detailed study the capillaries are found to contain an increased number of endothelial cells or polymorpho-

nuclear leukocytes. It is clear that the polymorphonuclear leukocytes are derived from the blood and when these cells predominate as shown in Fig 54 we may speak appropriately of exudative glomerulonephritis. But often the cells in the capillaries are all endothelial and it is clear that we are dealing with an early stage of acute diffuse proliferative glomerulonephritis (Fig 55). The capillaries are only partially obstructed and there are no intracapillary fibers as in clinical glomerulonephritis (see below).

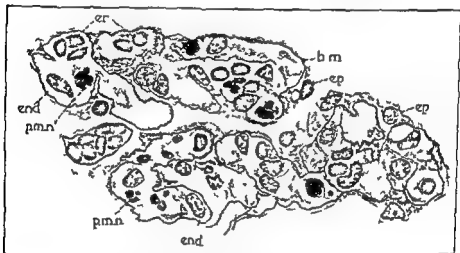


FIG 55 Early acute diffuse glomerulonephritis (non-clinical). From a case of lobar pneumonia. Azo-carbune stain. Drawing under high magnification. *b m* Capillary basement membrane *end* endothelial cell *ep* glomerular epithelial cell *er* erythrocyte *pmn* polymorphonuclear leukocyte.

**2 Typical Clinical Glomerulonephritis**—This may be subdivided according to the clinical course into acute, subacute and chronic. A clinical distinction between these three groups is useful but somewhat arbitrary. Pathologically the lesions in the three groups differ markedly in degree and extent but very little in quality. There are numerous transition cases between the groups both clinically and pathologically.

(a) *Acute Glomerulonephritis*—Acute glomerulonephritis practically always follows an acute infectious process of some kind. The infections most frequently giving rise to glomerulonephritis are sore throat and scarlet fever, but many other infections are occasionally responsible, viz. infected wounds, otitis media, empyema, peritonitis, etc. The symptoms of renal involvement commonly appear from one to three weeks after the onset of scarlet fever and a few days after a sore throat. The association of acute glomerulo-

nephritis with streptococcic and pneumococcic infections is so impressive that very few investigators doubt the causative relationship of these organisms to the disease.

The clinical symptoms vary with the severity of the disease. In

duration of entirely asymptomatic. The diagnosis may be made on the presence of edema, albuminuria and erythrocytes in the urine. In the absence of both edema and hypertension the diagnosis cannot be established.

20 to 40 mm Hg during the first few days, but it is often found normal in mild cases after this period. In severe cases hypertension is seldom absent. Oliguria is frequent and anuria may occur.

The majority of patients with acute glomerulonephritis pass through the acute stage within a few months. A few die of uremia after an acute or subacute course, and a great many pass on into an active or latent chronic stage. The majority of children recover completely, but it is believed that about 70 per cent of adults ultimately develop a chronic nephritis after a latent stage of many years' duration. Many of the soldiers who had acute nephritis during the World War and were thought to have recovered finally developed chronic nephritis after a latent period of from five to ten years.

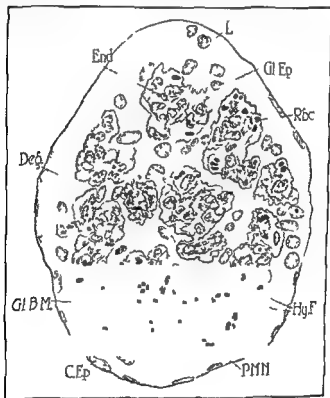
Macroscopically in the acute stage the kidneys are enlarged and cloudy. The external surfaces are smooth. There are no certain gross distinctions from a nephrosis, but glomerular hemorrhages are suggestive of nephritis.

Microscopic sections under low magnification show enlarged avascular glomeruli with an increased number of nuclei. The diameter of the glomerulus is often increased as much as 50 per cent. There is an enormous increase in the number of nuclei. With ordinary stains that do not bring out the capillary basement membrane it is very difficult to determine the source of the new cells, but when this membrane is stained as may be done with Heidenhain's modification of Mallory's aniline blue stain it is seen that nearly all the new cells lie within the membrane. In Fig. 76, which illustrates an early stage of acute glomerulonephritis, the detailed structure is shown. The glomerular epithelial cells have not increased and correspond with the normal except for a slight increase in size. There are only a few erythrocytes in the capillaries, the lumens being filled mainly with mononuclear cells. The mononuclear cells are for the most part attached to the capillary



walls and are interpreted as endothelial in origin but it is possible that some of them are mononuclear leukocytes from the blood. They fuse to form syncytial masses which distend the capillaries and leave little or no space for the erythrocytes.

A variable number of polymorphonuclear leukocytes are seen in the capillaries. Sometimes they are numerous but usually there are only a few as in Fig. 56. They are surrounded by endothelial cells and they usually show evidences of degeneration.



A prominent feature is the presence of numerous hyaline fibers which form a meshwork about the endothelial cells and leukocytes. The nature of these fibers has not been determined. They stain similarly to the capillary basement membrane and show numerous connections with it. They do not give the staining reactions of

fibrin. When first formed they do not give the staining reactions of collagen, but later on they stain like collagenous fibers. The increase in the number and size of these fibers is responsible for the hyaline appearance of the glomerulus in the later stages.

As the lesion becomes chronic, the intracapillary fibers increase

bare nuclei are left surrounded by hyaline material



FIG. 57.—Glomerular capillary loops from a case of chronic glomerulonephritis. *Azo-carmin* stain. The capillaries are enlarged and filled with endothelial cells and intracapillary fibrils. (Drawing) b.m. Basement membrane and endothelial nuclei; ep. epithelial cells; / network of intracapillary fibrils. (Bell's Text-book of Pathology.)

The fundamental change in glomerulonephritis is, therefore, occlusion of the capillaries by the growth of the endothelial cells, the formation of intracapillary fibrils and the accumulation of leukocytes. These processes may be called intracapillary glomerulonephritis.

The capsular epithelium sometimes proliferates extensively to form crescent-shaped masses which compress the glomerular tuft (Fig. 58). These are called epithelial crescents, and they are more frequently seen in fulminating cases. This process may be called extracapillary glomerulonephritis. The glomerular epithelium, *e. e.*,

the visceral layer, does not take an active part in the reaction. The pressure of an epithelial crescent may be the main cause of occlusion of the glomerular capillaries, but an intracapillary glomerulitis is always present.

One of the features of clinical acute glomerulonephritis is that it is diffuse, and it is commonly stated that every glomerulus is injured. However, a thorough study of the kidneys in acute cases will usually reveal some glomeruli in which there is very little capillary obstruction. It is easily determined that the capillary occlusion is extreme in some and only moderate in others. Apparently every glomer-

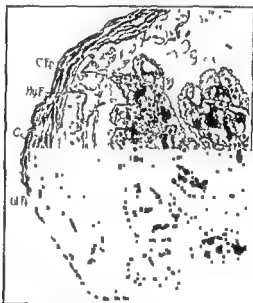


FIG. 58.—Chronic diffuse glomerulonephritis. Stain as in Fig. 56. Drawing by Leone McGregor. Lettered as in Fig. 56. The intracapillary fibers have fused to form solid hyaline masses (Hy) enclosing the endothelial nuclei. Some of the glomerular capillaries are permeable. An epithelial crescent is shown (C).

ulus is injured, but the degree of injury, as represented by closed capillaries, is variable.

subacute stage

Apparently no study has been made of the glomerular lesions in cases of acute glomerulonephritis that terminate in recovery. The

author has had the opportunity of studying one atypical case. This was a male child aged twenty-one months who had been suffering from otitis media for six weeks before admission. There was a purulent discharge from both ears. The temperature ranged from normal to  $100^{\circ}\text{F}$ . The leukocyte count varied from 16,000 to 37,000—the differential count showed 70 to 84 per cent polymorphonuclears. There was a trace of albumin in the urine and on one occasion numerous erythrocytes. There were many leukocytes in the urinary sediment. There was no edema. No blood pressure was recorded. One kidney was removed under an erroneous diagnosis of abscess or tumor. This is not a clinical picture of acute diffuse glomerulonephritis but one which would be interpreted as focal nephritis. The kidneys were cloudy and swollen. There was no pyelitis. The glomeruli are all involved. They are very cellular and anemic. There is a marked increase of endothelial cells in most of the capillaries and some capillaries are completely closed by endothelial cells and intracapillary filers. However the majority of the glomerular capillaries are patent. There are a few epithelial crescents. The child has subsequently recovered completely.

Notwithstanding the atypical clinical picture this case can only be interpreted as acute diffuse glomerulonephritis of mild degree. If we accept this case as representative of mild acute diffuse glomerulonephritis it is clear that recovery comes about because relatively few capillaries are completely closed.

The tubular epithelium in acute glomerulonephritis is always injured to some extent but the functional disturbance is chiefly due largely to obstruction of the glomerular circulation.

Often there is an exudate of leukocytes in the interstitial tissues about the glomeruli. Leukocytes and erythrocytes escape from the glomerular capillaries and enter the lumen of the tubules where they are often seen in large numbers. Hemorrhage occurs chiefly from glomeruli that have patent capillaries and are therefore much less damaged than occluded glomeruli that cannot bleed.

Acute glomerulonephritis occurred in epidemic form during the World War among the soldiers especially those in the trenches. It has been referred to as war or trench nephritis. There are no anatomical differences between war nephritis and acute glomerulonephritis as described above.

(b) *Subacute glomerulonephritis*. This group blends on the one side with the acute and on the other side with the chronic type. Subacute may be properly applied clinically to a case that terminates in uraemia after a duration of several months. The typical clinical picture is heavy albuminuria with casts and erythrocytes, marked edema, marked hypertension and progressive renal insufficiency.

At postmortem the kidneys are found enlarged and cloudy. The external surfaces are smooth and the cortices are somewhat increased in thickness. Microscopically the tubules all show a pronounced atrophy but very few have disappeared entirely (Fig. 59). The glomeruli are enlarged and bloodless. The capillaries are completely occluded by swollen endothelial cells, intracapillary fibers and leukocytes. Epithelial crescents are usually numerous. There are relatively few hyaline glomeruli. Lesions of this type probably begin as a severe injury to nearly all the glomeruli. The closure of the glomerular capillaries brings about a slow disuse

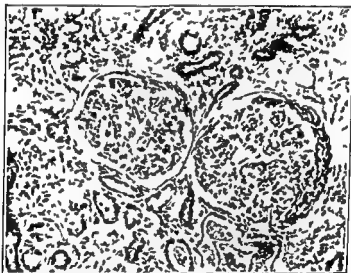


FIG. 59—Subacute glomerulonephritis. The glomeruli are enlarged and the capillaries are almost completely closed. The tubules show a rather marked atrophy. This appearance is found in all parts of the kidneys. There is no gross contraction of the kidneys. (Photomicrograph from Bell's Text-book of Pathology.)

atrophy of the tubules and a progressive failure of renal function. There is extensive tubular atrophy but the kidneys do not have sufficient time to contract as they do in chronic cases.

(c) *Chronic Glomerulonephritis*—This is a disease of slow development and long duration. The early stages are not well known since the patient seldom comes to our attention until the disease is far advanced. Only a few cases give a history of a definite clinical acute glomerulonephritis but it is nevertheless probable that at least a mild acute onset has occurred some years previously. The usual initial symptoms are weakness, dyspnea on exertion, headache, hypertension, edema of the ankles and albuminuria. The disease

is commonly present a long time before any definite symptoms develop

Some cases are discovered at a relatively early stage in the course of a routine examination for life insurance or other purposes. In these latent cases the symptoms and signs are less pronounced than in the active chronic case. There may be little or no edema, the blood-pressure is only slightly elevated or normal and anemia is not severe. Persistent albuminuria and casts call attention to the renal lesion.

The course of chronic glomerulonephritis is usually characterized by exacerbations and remissions. The exacerbations are brought on by colds, sore throat and other infections and result in aggravation of all the symptoms. During the remissions the patient improves sometimes to the point of complete disappearance of albuminuria. Renal function becomes progressively poorer in the course of the disease.

Albuminuria and casts are always present except in rare instances during remissions in mild cases.

Edema is variable. It is usually more pronounced during acute exacerbations and it is often absent over long periods. There is no definite relation between the amount of edema and the degree of renal insufficiency. Cases in which edema is prominent are often spoken of as the paraneurymatous or nephrotic type. Edema is influenced by the severity of albuminuria, the fluid intake, rest and the type of glomerular lesion and unknown factors.

Hypertension is nearly always present but may be absent in mild cases. The systolic blood pressure usually ranges between 140 and 180 mm Hg. It is not often above 200 mm Hg but has developed may have pressures above 200 mm Hg.

Renal function is not markedly impaired until extensive occlusion of the glomerular circulation has developed. Blood-urea nitrogen is normal or only moderately elevated until the final stage of the disease is reached. The excretion of phenolsulphonephthalein is definitely reduced before there is a convincing rise of blood urea nitrogen.

Secondary anemia develops along with renal insufficiency. In many cases of chronic glomerulonephritis as well as in some acute and subacute cases there is a decrease of plasma proteins, especially serum albumin and an increase of blood lipoids. These phenomena are usually more pronounced when edema is present. A decrease of plasma proteins may be found in other types of renal disease, e.g., lipid nephrosis, amyloid nephrosis, nephrosis of pregnancy and subacute nephrosis. It may also occur in diseases of extrarenal origin particularly lobular pneumonia and famine edema.

The decrease of plasma proteins may develop in the complete absence of edema as in lobar pneumonia. However, a severe edema is usually associated with low serum proteins, and when the serum albumin falls as low as 0.8 per cent, edema is almost invariably present.

**Macroscopic Appearance**—The kidneys in chronic glomerulonephritis are of two types: contracted and non-contracted. The latter belong to the lipoid nephrosis group, which will be discussed in a subsequent paragraph. The contracted kidneys together usually weigh from 100 to 200 gm.

Some are much smaller than others. In general, the smaller kidneys are found in the cases of longer duration. The capsules are adherent firmly, and the external surfaces are finely pitted. There are no cortical adenomas as in the hypertensive kidneys. On section the cortices are much thinner than normal and indistinctly delineated from the pyramids. The cortices usually have a brownish tinge—a feature of great value in distinguishing glomerulonephritis from hyaline-contracted kidneys.

**Structure**—A large percentage of the glomeruli are hyaline (Fig. 60), in some instances as high as 90 per cent. The tubules associated with such glomeruli have either disappeared entirely or they are represented by small epithelial cords. The surface of the kidney over such areas is depressed, giving the pitted appearance. The increase of fibrous tissue in the atrophic areas is largely relative.

The tubules that have not undergone atrophy are associated with glomeruli that are enlarged but not hyaline (Fig. 60). These glomeruli show an increase of capillary endothelium but the capillaries are not completely obstructed (Figs. 57 and 58). In the final stages of chronic glomerulonephritis the few glomeruli that persist show partial occlusion of their capillary circulation. The



Fig. 58. Chronic glomerulonephritis. The tubules associated with the hyaline glomeruli have practically disappeared. The large glomeruli have a histological structure similar to those shown in Figs. 57 and 58. The tubules associated with the large glomeruli are fatty. Photomicrograph.

persistent convoluted tubules are dilated and show a variable amount of fat in their cells.

*Pathogenesis* — As stated above only an occasional case of chronic glomerulonephritis begins as a typical acute clinical case. In the vast majority the immediate inciting cause is unknown. The most convincing evidence that the disease is inflammatory in origin is the histological structure of the glomerular lesions. The

morphonuclear leukocytes are also found imprisoned in the closed capillaries. Epithelial crescents are seen frequently. The chief difference between acute and chronic stages is due to increase and fusion of intracapillary fibers.

The atrophy of the tubules is closely related with the occlusion of the glomerular capillaries. It is clearly a disuse atrophy and not the result of anemia. The capillaries among the tubules anastomose freely and open capillaries are regularly seen between atrophic tubules.

*The Arterioles* — The afferent glomerular arterioles frequently show small areas of hyaline degeneration in acute and subacute cases and in occasional chronic cases of many years duration a high degree of arteriosclerosis may be found. In such instances a clinical distinction from primary hypertension can hardly be made but a careful microscopic study will disclose the character of the lesion.

**Subgroup Lipoid Nephrosis** Lipoid nephrosis is not a new disease. In the older literature it was known as parenchymatous nephritis. It was brought to our attention by Volhard and Fahr in 1914 as genuine nephrosis. Epstein in his extensive studies on this disease referred to it as chronic nephrosis. The term lipoid nephrosis suggested by Munk has apparently supplanted the other terms in the current literature.

The clinical features of a typical case of pure lipoid nephrosis are the presence of severe albuminuria with cysts oliguria, marked edema, hypercholesterolemia and decrease of the plasma proteins.

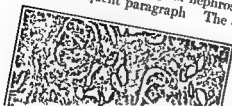
Unfortunately above mentioned less prominent published reports indicate that about 50 per cent recover ultimately, although albuminuria may persist for several years. About one-half of the



The decrease of plasma proteins may develop in the complete absence of edema as in lobar pneumonia. However, a severe edema is usually associated with low serum proteins, and when the serum albumin falls as low as 0.8 per cent, edema is almost invariably present.

**Macroscopic appearance**—The kidneys in chronic glomerulonephritis are of two types, contracted and non-contracted. The latter belong to the lipoid nephrosis group which will be discussed in a subsequent paragraph. The contracted kidneys together usually weigh from 100 to 200 gm.

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Contracted kidney in chronic glomerulonephritis. The tubules associated with the hyaline glomeruli have practically disappeared. The large glomeruli have a histological structure similar to those shown in Figs 57 and 58. The tubules associated with the large glomeruli are fatty. Photo micrograph.

areas previously occupied by tubules and the surface of the kidney over such areas is largely relative. The increase of fibrous tissue in the atrophic areas is largely relative.

The tubules that have not undergone atrophy are associated with glomeruli that are enlarged but not hyaline (Fig 60). These glomeruli show an increase of capillary endothelium, but the capillaries are not completely obstructed (Figs 57 and 58). In the final stages of chronic glomerulonephritis the few glomeruli that persist show partial occlusion of their capillary circulation. The

large percentage of the glomeruli are hyaline (Fig 60), in some instances as high as 90 per cent. The tubules associated with such glomeruli have either disappeared entirely or they are represented by small epithelial cords. The hyaline glomeruli are shrunken and contracted, giving the kidney a pitted appearance.

persistent convoluted tubules are dilated and show a variable amount of fat in their cells

*Pathogenesis* — As stated above only an occasional case of chronic glomerulonephritis begins as a typical acute clinical case. In the vast majority the immediate inciting cause is unknown. The most convincing evidence that the disease is inflammatory in origin is the histological structure of the glomerular lesions. The lesions can only be interpreted as the outcome of acute glomerulitis. A comparison of the acute stage shown in Fig. 56 with the chronic stages shown in Figs. 57 and 58 brings out this relation. In the chronic stage the endothelial cells are still prominent but they are compressed by a great increase in the intracapillary fibers. Polymorphonuclear leukocytes are also found imprisoned in the closed capillaries. Epithelial crescents are seen frequently. The chief difference between acute and chronic stages is due to increase and fusion of intracapillary fibers.

The atrophy of the tubules is closely related with the occlusion of the glomerular capillaries. It is clearly a disuse atrophy and not the result of anemia. The capillaries among the tubules anastomose freely and open capillaries are regularly seen between atrophic tubules.

*The Arterioles* The afferent glomerular arterioles frequently show small areas of hyaline degeneration in acute and subacute cases and in occasional chronic cases of many years duration a high degree of arteriosclerosis may be found. In such instances a clinical distinction from primary hypertension can hardly be made but a careful microscopic study will disclose the character of the lesion.

*Subgroup Lipoid Nephrosis* Lipoid nephrosis is not a new disease. In the older literature it was known as parenchymatous nephritis. It was brought to our attention by Volhard and Fahr in 1914 as genuine nephrosis. Lyslein in his extensive studies on this disease referred to it as chronic nephrosis. The term lipoid nephrosis suggested by Munk has apparently supplanted the other terms in the current literature.

The clinical features of a typical case of pure lipoid nephrosis are the presence of severe albuminuria with cysts oliguria, marked edema, hypercholesterolemia and decrease of the plasma proteins

indicate that about 50 per cent recover ultimately although albuminuria may persist for several years. About one-half of the

deaths are due to peritonitis and the rest to other infections. Uremia does not develop.

Pure lipid nephrosis is usually defined anatomically as follows. The enlarged kidneys show smooth external surfaces and thickened cortices of light yellowish color. Microscopically the tubular epithelium contains a variable number of lipid droplets and the glomeruli are practically normal.

Nearly all observers describe the glomeruli as normal or practically normal and it is this feature which is believed to distinguish lipid nephrosis from chronic glomerulonephritis.

The idea that the glomeruli are normal has given rise to the widespread opinion that lipid nephrosis is not a primary disease of the kidney but a general metabolic disorder with secondary renal changes.

If rigid clinical criteria are applied and no cases are included which show any elevation of blood pressure or evidence of renal insufficiency, lipid nephrosis in adults becomes a very rare disease. However, one frequently sees cases which correspond to lipid

hypertension or  
nephritis with  
are thoroughly a  
nephrosis is studied the more frequently it is found to correspond with the mixed type. In children the clinical picture of pure lipid nephrosis is not especially rare. Occasionally a disease that appears to be a pure nephrosis later becomes a definite glomerulonephritis.

A microscopic section of a pure lipid nephrosis is shown in Fig 61. Under low magnification the glomerulus does not appear markedly abnormal but under high magnification it is seen that the capillaries are partially obstructed by new cells. The extent

with endothelial cells\*. The newly formed endothelial cells are so filled with lipid droplets that they are barely visible in routine preparations. In another case of pure lipid nephrosis described in the paper just referred to there was partial obstruction of some of the capillaries by endothelial cells and an uneven thickening of the capillary basement membrane.

In many cases reported in the literature in which the glomeruli are described as normal it appears probable from the accompanying illustrations that definite glomerular alterations could have been demonstrated with appropriate technique. Fahr\* in his latest pub-

\* See Am J Path. vol 5 Plate 106 Fig 9 1939

lication on nephrosis illustrates hyaline thickenings of the walls of the capillaries. But it must be admitted that instances of lipoid nephrosis occur in which the glomerular alterations are minimal *e. g.* "Amberg" case and one of Klemperer's cases. Even when no structural changes are demonstrable there must however be an

followed by endothelial reaction and resulting capillary obstruction the clinical picture is that of nephritis but in the absence of reaction or with incomplete capillary obstruction the resulting clinical picture is nephrosis. This interpretation gives a simpler explanation of the mixed type than the assumption that we are dealing with two diseases—nephrosis and nephritis mixed in varying proportions. It also affords an easy explanation for the observation that a nephrosis frequently passes over into a nephritis—the capillary obstruction becomes more pronounced.



FIG. 61. Pure lipoid nephrosis. Low magnification. The tubules are somewhat dilated and they show many lipid droplets in the cytoplasm. The glomeruli show some capillary obstruction. Photomicrograph.

The nephroses of mixed type (nephritis with nephrotic tendency) all show pronounced glomerular changes. The kidneys are not contracted. The tubules show a moderate degree of atrophy as is indicated by the increased space between them and there are numerous lipid droplets in the cytoplasm. In the glomeruli there is sometimes an endothelial increase with intracapillary fibers as in typical glomerulonephritis but more often the structure is such as is shown in Fig. 62. The walls of the capillaries are thicker and their lumens are narrowed. With the Mallory-Heidenhain stain it can be seen that the narrowing of the capillaries is largely due to massive thickening of the capillary basement membrane.\*

\* See *Am. J. Path.* vol. 5, Plate 108, Figs. 4 and 6, 1929.

In cases of lipoid nephrosis of mixed type that terminate in uremia the glomerular capillaries are gradually obliterated by thickening of the basement membrane the glomerulus is no longer permeable to blood and the tubule undergoes atrophy. A fairly advanced stage of this process is shown in Fig. 63. It is surprising that thickening of the capillary basement membrane is associated with increased permeability to proteins but very high magnification of thickened membranes discloses numerous irregular spaces in their substance in fact thickened membranes have a porous structure which cannot be seen in the normal membrane.

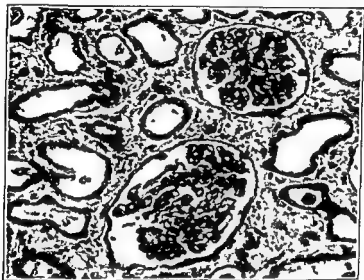


FIG. 63.—Nephritis with nephrotic tendency. Low magnification. Stained with iron hematoxylin. The glomerular capillaries are narrow and many are completely closed. The tubules are dilated and show an early stage of atrophy. (Photomicrograph from Bell's Text-book of Pathology.)

The mixed type of lipoid nephrosis is described under various names: 1) hydropic type of glomerulonephritis; nephrotic type of glomerulonephritis; and parenchymatous nephritis. The kidneys differ macroscopically from those of the azotemic or ordinary type of glomerulonephritis in that they are large and fatty and not contracted as in the latter. Microscopically the glomerular capillaries in the nephrotic type are narrowed but not completely obstructed and tubular atrophy is therefore not pronounced. The narrowing of the capillaries is brought about in most instances by thickening of the basement membrane but endothelial increase is often a minor and sometimes a major factor. The open capillaries with their porous membranes allow the continuous escape of serum

proteins in the urine with resulting edema and hypercholesterolemia. It is therefore this structural difference in the glomerular lesions which brings about the clinical differences between hydropic and azotemic glomerulonephritis.

It does not clarify our conception of this renal lesion to regard it as a mixture of two diseases — nephrosis and nephritis. It may be interpreted more simply as a form of glomerulonephritis with alteration of the capillary walls but incomplete capillary obstruction.

The pure type of lipoid nephrosis is interpreted as injury of the glomerular capillaries with less pronounced structural changes. There are so many transitions between the pure and mixed types both clinically and anatomically that it is hardly possible to interpret the pure type as a distinct entity.



FIG. 1

f

FIG. 2

inflammatory process

Neither the clinical nor the pathological conception of this type

ular external surfaces and in the remainder there is more or less decrease in size with granular surfaces. In only about 15 per cent is there sufficient atrophy to warrant the term contracted kidney. The term primary contracted kidney is used somewhat arbitrarily to designate hypertensive kidneys that show a high degree of atrophy.

On microscopic examination 90 per cent of the kidneys from cases of primary hypertension show sclerosis of the afferent glomerular arterioles. The small arteries immediately preceding these arterioles are diseased in 98 per cent, but disease of these vessels occurs also in non hypertensive cases. In 10 per cent the disease has not extended into the afferent glomerular arterioles.



FIG. 64 — Arteriolosclerotic kidney: Longitudinal section of an afferent glomerular arteriole showing a subintimal deposit of hyaline. Photomicrograph.

In arteriolosclerosis the structural changes consist in a subintimal deposit of a hyaline material (Fig. 64). The hyaline is deposited in a layer of uneven thickness. As it increases in amount it tends to cause atrophy of the muscular layer and narrowing of the lumen. The hyaline deposit sometimes extends out into the tuft. The first change observed in the glomerulus is a thickening and wrinkling of the capillary basement membrane (Fig. 65). The arteriolar lesion precedes that in the glomerulus. As the arteriole becomes narrowed the glomerular capillaries collapse and the basement membrane increases until the entire glomerulus assumes a compact,

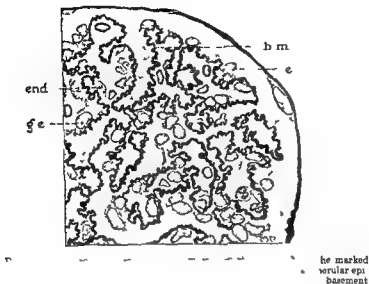


FIG. 66 Small renal artery in primary hypertension. Elastic tissue stain. Note the marked thickening of the intima due to increase of elastic tissue and the atrophy of the media.



shrinks and the surface of the kidney becomes pitted. Renal insufficiency develops when the atrophy becomes pronounced. Sclerosis of small arteries is as important as arteriosclerosis in causing atrophy and renal insufficiency.

Sclerosis of small arteries consists mainly in a great increase of elastic tissue in the intima (Fig. 66). This is called hyperplastic elastic intimal thickening. It is interpreted as a compensatory phenomenon resulting from increased intravascular pressure. The media of these arteries undergoes atrophy.

**Hypertension With Uremia**—Approximately 10 per cent of the deaths from primary hypertension are due to uremia. The usual case is a chronic hypertension with slowly developing uremia. In this type uremia is due to a gradual occlusion of small arteries and arterioles. In about one-fourth of the cases, uremia develops

uremia; a number of glomeruli show acute glomerulitis. This has been regarded as distinctive of uremic hypertension (Fahr), but McGregor found occasional glomeruli of this type in all forms of hypertension.

By no means all cases of hypertension with uremia are terminating in type. The expression "fulminant hypertension" seems more appropriate to designate hypertension with rapid development of uremia. Acute uremia in the course of hypertension may be due to a superimposed infection.

It is believed that primary hypertension begins as a generalized spasm of arterioles. The existence of arteriolar spasm is readily demonstrated in early cases by the fall of blood pressure which occurs during sleep and under the influence of amyl nitrite. In the more advanced types this relaxation cannot be brought about. It

resulting from which we cur readily developed

This hypothesis does not explain the intensity of arteriosclerosis in the kidneys and its usual absence in many regions, notably the skin and the muscles. On the other hand, if we adopt the theory that arteriosclerosis of the kidney is the primary lesion and that

hypertension is of reflex origin we are unable to explain those cases without renal arteriosclerosis.

It is important to distinguish chronic glomerulonephritis from primary hypertension with uremia whenever possible since the two diseases are entirely different in etiology. Clinically, chronic glomerulonephritis shows moderate cardiac hypertrophy and hypertension edema albuminuria secondary anemia and a slowly developing uremia. Cardiac decompensation is rare. Cases of many years duration may develop very high blood pressure extensive arteriosclerosis and retinitis. This type can hardly be distinguished clinically from primary hypertension. At postmortem the kidneys show granular surfaces but small subcapsular adenomas are unusual. On section the cortices are yellowish. Microscopically there are evidences of old glomerulitis which are readily recognizable unless arteriosclerosis is extreme.

Primary hypertension is readily distinguished clinically from chronic glomerulonephritis except in the cases which develop renal insufficiency. These may present some difficulty. Primary hypertension is suggested if there is at any time definite evidence of cardiac failure apoplexy or coronary disease. The eyegrounds are usually characteristic. Marked enlargement of the heart and very high blood pressure also indicate primary hypertension.

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## CHAPTER XIX

### CONGENITAL RENAL ANOMALIES

By STANLEY P. REIMANN, M.D.

**Introduction & Factors Responsible for Renal Anomalies**—Congenital anomalies are usually explained on the basis of the normal developmental course of the kidney and ureter. This presupposes a definite and settled knowledge of their embryology; otherwise controversies in the latter will be carried over into the former. At the present time, however, it is not sufficient merely to describe these deviations from the normal in anatomical terms and relate them to anatomical embryological considerations; for during the past decade there have accumulated data in genetics and experimental embryology, or as it is sometimes called developmental mechanics, which allow the introduction of physiological concepts and even a few chemical terms.

The possibilities are overwhelmingly in favor of the view that the structural elements which transmit species specificity as well as individual peculiarities are contained mostly within the chromosomes. But the cytoplasm also is not to be neglected in this consideration. The probabilities are that the human ovum is at least partially regulatory, which means that slight defects acquired before or shortly after fertilization do not determine a defective adult. In other words, the ovum can regulate or compensate for and overcome some defects with the ultimate production of a perfect individual. In this process, and in normal development also, the phenomena of organizers, as discovered and elaborated particularly by Spemann and his school, can be applied to the kidney as well as to other organs.

Briefly, the organizer phenomena are as follows. In the segmenting ovum, but little differentiation of the oncoming cells is discern-

hand are divided absolutely equally between all cells. In developing embryos of such animals as sea urchins, tritons, etc., which can be observed readily, a few cells may be seen then in a region called the dorsal lip. When these cells appear, a profound change

takes place in the whole embryo cell division is retarded and differentiation and organization receive a great impetus. The embryo soon takes on definite structure and begins to look like something. Then cell proliferation is again accelerated whereupon the previously differentiated parts in their turn act as organizers and guide the newly produced cells into the channels proper for the particular time and of course kind of embryo. The new cells being differentiated act as organizers on their own account and so on.

Probably the embryo has now reached a size where simple contact and diffusion are inadequate for communication between cells and for regulating and integrating their activities hence nerves are developed which flash messages to and fro and thus govern the growth as a whole. Later genuine ductless glands are added as cells are differentiated for their production and these also act as coordinators. All these factors together plus the developing and organizing influence of function as it is begun by tissues as well as doubtless many other factors lead the growth into the proper differential relations so that a liver does not grow too big for the heart the heart remains the proper size for the lungs etc. Furthermore the structures are also developed in tune with those of the lineage from which the embryo arose.

All through this process the chromosomes act as guides and probably also as restrainers. That is living protoplasm is capable of infinite variation the chromosomes restraining this unlimited potency and forcing the organism to remain species specific and individual. Hence in any comprehensive study of kidney anomalies we must consider chromosomes cytoplasm organizers and other guides such as nerves bloodvessels probably enzymes hormones and many other chemical substances.

If the chromosomes determine congenital anomalies then they should be hereditary in every sense of the word and should behave in succeeding generations according to Mendel's laws. That certain anomalies are produced by these means is attested by human hereditary studies wherein such things as horseshoe and polycystic kidneys have been shown to occur in numerous members of a family.

When trouble arises in the cytoplasm as a cause of congenital anomalies modern genetics says this also can be hereditary (Little<sup>17</sup>). On the other hand it is easier to imagine acquired defects in the cytoplasm than in the chromosomes. Acquired changes in chromosomes are called mutations and the possibility of a mutation occurring in a fertilized ovum coming from healthy parents cannot be overlooked as another cause of kidney anomalies.

Trouble from organizers nerves chemicals etc. are more probably acquired. And even though we know little of the details of

such troubles nevertheless Stockard for instance has obtained congenital anomalies by varying the oxygen tension. Other workers report the production of various abnormalities even monstrous

### SPECIFIC EXAMPLES OF CONGENITAL RENAL ANOMALIES

The first to be discussed is naturally the anatomy of embryonic development. Two ideas one of which has been almost discarded are current in respect to the subject. The one most generally believed is that the kidney and ureter are developed from two separate anlagen the cortex and glomeruli and tubules to collecting tubules from one (the so-called renal blastema) and the pelvis of the ureter and collecting tubules from the other (the uterine bud which arises after the union of the Wolffian duct and the cloaca). The two developing structures meet and junction is effected so that the convoluted tubules of Henle come into a continuous system from glomerulus to pelvis. Failure of proper union of a few or many results in the common congenital anomaly of cystic kidney with many or few cysts accompanied by a corresponding reduction in the number of tubule systems in working order. The practical aspect consists almost entirely in how many of these tubule systems are workable that is again a question of kidney function in respect to the number of active units.

Occasionally a polycystic kidney may be large enough or even be displaced so as to produce pressure on neighboring organs such as gall bladder bile ducts colon etc. The matter of pressure of the cysts on what normal kidney tissue exists is also no doubt of utmost importance the maintenance of life depending on preserving the integrity of what tubule systems are present. Such individuals also should be protected more than ordinarily against colds infection etc. and in woman extra care during pregnancy both because of the additional physiological strain and because of pressure from the growing uterus.

When either the renal blastema is hindered from developing or the kidney is hindered from developing no kidney is formed. Boyden<sup>2</sup> believes that failure of the ureter (three fourths of cases) and seldom if ever of the renal blastema itself.

Thus for the production of kidney anomalies are obtained anatomical explanations from the embryology. Since they

appear in standard textbooks they will be alluded to here only in the wealth of knowledge of the mode of production of which is still obscure. As an example may be cited the discussion of Boyden<sup>1</sup> of the role of the circulation in horseshoe kidney: *i. e.* whether the anomaly itself organized vessels not ordinarily appearing in ontogeny or whether

theories which have been advanced for their formation—those dealing with extrinsic causes and those that attribute fusion to deviations that are inherent in the primordia of the kidneys. He illustrates the second group by the theory that two ureters may

bifurcation of the aorta into umbilical or common iliac arteries. This bifurcation forms a U shaped crotch in which the kidneys are lodged and from which they escape by migrating upward. The arteries, as a mechanical obstruction, tend to bring the right and

the lower poles in which case the horseshoe would be convex inferiorly.

organs or vessels occasionally demands relief: a displaced horseshoe kidney, for instance, having been known seriously to obstruct labor (Bugbee<sup>2</sup>).

## STATISTICAL STUDIES ON CONGENITAL RENAL ANOMALIES

Dimension of Renal Type as Related to Clinical Outcome

Unilateral absence occurs about once in 900 autopsies (Eisen-drath<sup>3</sup>, Campbell<sup>4</sup>, Thompson<sup>21</sup>).



organs arising from this early indifferent structure such as those mentioned above. When one ureter ends blindly stenosis and atresia are the results with possible hydronephrosis or pyonephrosis. Graves and Davidoff<sup>9</sup> relate that the ureter of a cat passed in back of the inferior vena cava then medial to it and then crossed it anteriorly. They found 3 human cases in the literature in which a similar condition occurred. 1 in an infant aged a few weeks. 1 in a man aged fifty five years and 1 in a man aged eighty four years. There was hydronephrosis in each case.

**Vascular Anomalies**—Renal anomalies in structure and position are practically always accompanied by anomalies in the vessels. The question arises therefore Are the former determined by the latter or the latter by the former. A positive general answer is

kidneys migrate from their low position they acquire their blood supply from a new source. Thus the vessels in the adult kidney have been known to come from the lower aorta from an iliac artery even from the inferior mesenteric artery. The venous relations are also variable.

Lisa and Levine in 1200 autopsies found the following. 1 case in which the left renal vein passed posterior to the aorta. 1 case in which there was a double right renal vein. 8 cases in which there was a double renal artery on one side. 2 cases in which there were double renal arteries on both sides. 2 cases in which the renal artery entered at one pole of the kidney.

Accessory vessels are fairly common usually entering the lower pole. They are usually smaller than the main vessel but may be of equal size or even larger. Practical aspects consist in possible torsions or compressions with resulting damage to kidney substance and also in operative procedures when vessels should not be blindly clamped and tied but identified first and the kidney mobilized to make certain no accessory vessels have been missed.

## CLINICAL CONSIDERATIONS OF RENAL ANOMALIES

Viewed as a whole there is unanimous agreement that the anomalous kidney is more subject to disease than the normal organ. Data as to the various forms of Bright's disease are not as definite as those which show that the so-called surgical conditions are more common. Under this are included stone formation (kidneys and ureter) hydronephrosis pyonephrosis perhaps tubercu

estimated to be about 1 in 900. The figures as to relative rates of



tumor formation in normal and anomalous kidneys and ureters leave the question open

The congenitally abnormal kidney may give no symptoms at all, ordinarily it is one of the complications which lead to its discovery, such as pressure symptoms on surrounding organs, pain and discomfort from distentions and compressions and calculi, the appearance of a mass in polycystic kidneys or in hydronephroses or pyonephroses. The urine also may show no abnormalities until complications arise, whereupon pus, blood and gravel appear, or casts and the other signs of infections, injuries and perversion of function

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## CHAPTER XX

### INFECTIONS OF THE KIDNEY

By HOBART A. REIMANN M.D.

**Introduction** —Although the word nephritis connotes inflammation of the kidney it is used by common consent in a rather limited sense and applies to degenerative or vascular terms as pyelitis pyelonephritis pyelonephrosis abscess and so on according to the anatomical character or distribution of the lesions. It is with lesions of this type that this chapter deals.

**Classification** Much depends upon point of view in the classification of infections as to whether the author is a pathologist bacteriologist or clinician. It is obvious also that no two authors will agree completely on any one classification which is so well illustrated in the decades of controversy regarding nephritis itself. Furthermore the function of classification is often only to preserve some degree of order in formal presentation and to establish some uniformity in nomenclature for the purpose of a common basis for discussion. In regard to infections of the kidney the pathological classification in current use is unsatisfactory unless qualified by terms indicating the specific etiological focal or urogenital factors involved. Renal infections have been classified further on the basis of the pathway of infection to the kidney whether it be arterial ascending through a column of urine impounded in the ureter

infections in a previously normal kidney resulting from the lodgment of virulent organisms and as infections resulting from the deposition of any of a variety of organisms in a kidney the resistance of which has been reduced by some urogenital abnormality or condition.

It seems that all of these methods of classification are inaccurate and unsatisfactory. It is highly desirable therefore to decide upon a classification which will qualify some of the terms in common use by terms indicating the etiological agent wherever possible. It is doubtless of greater importance to know the actual etiological

agent its source of origin and the natural history of the infection it induces than to devote efforts in determining the gross and microscopic pathological changes or even the route of infection it traverses in reaching the kidney. It would be most desirable to establish diagnosis on a purely etiological basis as suggested forty years ago by T. Müller and later by Fahr<sup>29</sup> and others<sup>17,31</sup> but certain factors often render this procedure difficult. Unless the organism causing the infection can be isolated directly from the lesion as it exists in the kidney during life or in pure culture from the urine the situation is somewhat analogous to the same problem in pneumonia. Examination of the sputum in the latter case may at once reveal the etiological agent but often a mixture of organisms is present and only by special methods can the pathogen in question be identified. Similarly examination of the urine may also promptly settle a

one causing the infection will be found in the urine. It seems best therefore to view the disease picture as a whole regarding the possible foci of infection, clinical course of the illness and physical signs and to correlate these with careful microscopic and bacteriological examinations of the urine and the information obtained by modern methods of urological examination. In many instances a knowledge of the natural history of an infection including its portal of entry or focus of infection will be of great assistance in diagnosis and rational therapy. The classification adopted for this presentation is based on one proposed by Hinman<sup>31</sup> and is satis-

TABLE 24. CLINICAL-ETIOLOGICAL CLASSIFICATION OF RENAL INFECTIONS

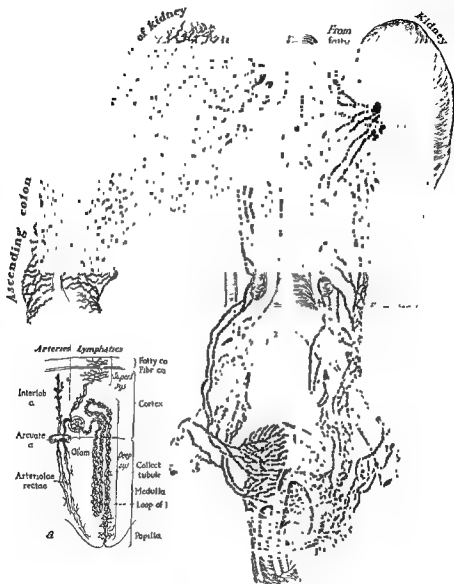
1. Specific infection of kidneys previously normal		2. Infection with organism as mentioned in Groups I and II, most commonly colon bacilli or streptococci as a result of dissemination of the kidney due to
Group I. Focal from portal of entry elsewhere in the body. Characteristic manifestations of the disease in the kidney. Infection with	Group II. Focal or metastatic from infection elsewhere or from general systemic disease. Characteristic manifestations of disease elsewhere	1. Urinary obstruction or glomerular structure as one neoplasm, pyelomyoma or other obstruction at any point of the urinary tract, faulty excretion of the blood or congenital malformations or metastatic infection from lower respiratory tract by varicose veins. Contaminations type so called sepsis in infants leukoemia, syphilis, malaria or deformation urethritis.
A. Bacilli of colon typhoid group	A. Bacterial infections	Traumatic infections from foreign body, contact with penicillin, chemical trauma followed by bacteremia
B. Staphylococcus	B. Coccal infections	
C. Tubercle bacillus	C. Filamentous infections	
D. Treponema pallidum	D. Syphilitic infections	
E. Gonococcus	E. Protozoal and metazoal infections	
F. Actinomyces	F. Fungal infections	
G. Echinococcus, etc.	G. Bickett's infections	

**Pathogenesis**—The kidneys have no free communication with the external environment. Infection obviously is almost invariably conveyed to the kidneys from some focus elsewhere in the body by routes to be discussed. The chief portals of entry of infection are (a) The urogenital tract (b) the gastro intestinal tract following appendicitis cholecystitis colitis or constipation (c) the respiratory tract following sinusitis for example and (d) miscellaneous foci elsewhere or systemic infectious disease. The importance of colds and upper respiratory infections as causative factors has been greatly minimized by the studies of Helmholtz although numerous examples are cited<sup>18</sup>. The part played by teeth and tonsils as foci of infection for *Streptococcus viridans* has been greatly exaggerated.

The pathways by which infection is conveyed to the kidneys have been the subject of controversy for decades. It appears that the commonest routes are by way of the blood stream the ureters or the lymphatics. Infection by contiguity and by penetration is less frequent.

**Hematogenous Infection**—Bacteria are present in the blood stream much more frequently than has been realized. Under ordinary circumstances they are usually harmless and the kidneys or any other organs if normal are unaffected. If however the bacteria are especially virulent or if the resistance of the kidney is diminished by any of the factors about to be considered the likelihood of the localization of infection and production of lesions is greatly enhanced. Bacteria reaching the kidney through the arteries either lodge as emboli in the capillaries and multiply if conditions are suitable or they may pass through the secreting membrane.

Observers thereafter showed that particles as large as bacteria do not pass through the membranes of a normal kidney. The question is still open. Brewer believed that a small number of avirulent organisms can pass the barrier. Dyke<sup>2</sup> on the other hand showed that staphylococci passed through only after lesions had been produced. Similar results with other organisms are reported by Helmholtz<sup>19</sup> Beacham<sup>20</sup> Book<sup>21</sup> Montgomery<sup>22</sup> and others. The matter is of especial importance in tuberculosis of the kidney in which unfortunately differences of opinion also exist. For the most part it appears that the resistance of kidney the factor of greatest importance<sup>23</sup> must first be diminished by mechanical obstruction by congenital abnormality by the deleterious effects of products liberated in general infections as they are excreted or by lesions produced locally in the renal capillaries by infection before bacteria appear on the distal side of the secreting membrane. The site of



within the kidney.

the earliest lesions in hematogenous infection may be in the renal cortex in the region of the convoluted tubules or in the central portion of the papillæ (pyelonephritis). The primary lesion may of course be found in the pelvis of the kidney where the bacteria may be first deposited by the blood stream (pyelitis) (Fig. 67). These facts emphasize the complexity of the problem and the difficulty of

infection in certain cases does reach the kidney (a) Through a column of urine impounded in the bladder and ureter either by growth and spread of bacteria through the fluid itself or by anti-

bilities just cited always complicates the question. This is illus-

tance of the kidney to infection from any source. The colon bacillus is most frequently encountered and is responsible for 80 or 90 per cent of infections of the ascending type.

produced kidney infections in dogs by merely cutting the ureterovesical valves. Lesions developed in this case without evidence of back pressure and only on the side on which the valves were cut.

**Lymphatic Route** In the opinion of many observers the lymphatics play a minor role in carrying infection to the kidney. It must be admitted however that in a portion of cases an ascending channel includes the cervix of the

Fig 67 Infection in any of these sites could conceivably reach the kidney through the anastomosis of lymph vessels and reversal of the normal lymph flow. Infection has been traced from the bladder to the kidney pelvis through the ureteral lymphatics both clinically and experimentally<sup>460</sup>. The lymphatics no doubt, play a large rôle in the spread of infection within the kidney. An intricate intercommunicating network exists in the cortex and medulla which communicates with the lymphatics of the pelvis and with those of the capsule (Fig 67, insert a).

**Direct Infection**—Direct infection may occur by penetration of the capsule itself by infection in adjacent tissues or organs, by per-

of  
is the cause or the effect of renal infections is still disputed. It would seem that in the majority of cases the presence of any foreign body tends to reduce the local resistance and to predispose to infection. On the other hand long standing infection with stasis and inspissation of the exudate and débris possibly results occasionally in ultimate encrustation or petrification.

**Bacteriology**—Table 29 represents the incidence of various bacteria as found in renal infections by various observers.

TABLE 29

	Sehe de mantel	Cabot and Crabtree	Lenharts	Woss die	Kretsch mer	Hellström
Colon bacilli	85	4	66	79	133	133
Staphylococci	2	23		34	29	40
Streptococci		4		34	1	6
Colon bacilli and staphylococci					10	24
Colon bacilli and streptococci						1
Staphylococci and streptococci		3			2	1
Cocci and bacilli		25				
Paratyphoid bacilli	1		3			
Gonococci	2			5		
Proteus bacilli	3		2			
Proteus and colon bacilli			1			
Influenza bacilli	2					
Cocci	5					
Other forms				35		24
No bacteria or unknown					27	13
Total	100	59	72	187	200	242

The tubercle bacillus is not included in the table since renal tuberculosis is usually regarded as a separate entity and not considered with other infections. Tuberculosis of the kidney in this presentation takes its relative place among other specific infections

*blastomyces, Amoeba histolytica, echinococcus and others*

### SPECIFIC INFECTIONS OF KIDNEYS PREVIOUSLY NORMAL

**GROUP I — Infections With Chief Manifestations of Disease in the Kidneys** — The kidneys involved in the specific infections discussed in Groups I and II were presumably normal previously. Infection occurs because of the recent diminution of the resistance of the renal tissues and growth of the organisms in question.

**Infection Due to Bacilli of the Colon Group (Acute Pyelitis, Pyelonephritis, Chronic Pyelonephrosis)** — This comprises by far the largest proportion of kidney infections. It is probable, however, that the figures given in certain statistics are somewhat too high, if primary infections are indicated, since in certain instances colon bacilli invade the tissues only after the field has been prepared, so speak, by primary infection due to other organisms. The primary

especially in infants and in women, which may in part be due to the proximity of the urethral orifice to the source of colon bacilli from the anus, (b) the vast surface presented by the intestinal tract as a potential portal of entry of colon bacilli into the blood stream, (c) all of the factors represented in column 3 of Table 28. Several factors not embodied in the table include various inflammatory diseases of the digestive tract as appendicitis, cholecystitis, colitis as well as constipation and hemorrhoids. Colon bacillus bacteremia is commonly present after operative manipulation or disease of the lower urinary tract. Scott<sup>21</sup> found *B. coli* in the blood in 40 per cent of his cases in which the urethra was the most probable portal of entry. *B. coli* sepsis occurs more frequently than is generally believed in women during the child-bearing period and in men past middle life, corresponding with the increased number of infections of the genital and urinary tract.

primary lesions occur in the kidney infected with colon bacilli



these cases were lesions present in the renal parenchyma. Since the pelvic mucous membranes were solely involved he regarded these as cases of ascending infection. Wilson and Schloss<sup>55</sup> however believed that severe pyuria in infants usually represents inflammation of the interstitial tissue. Chown<sup>19</sup> and Rosenbusch<sup>56</sup> expressed similar views. Gohrbandt<sup>58</sup> and others have shown that pyelitis and pyelonephritis seldom occur separately. Kennedy<sup>46</sup> studied the kidneys of animals injected intravenously with colon bacilli and in some infected by intraureteral inoculation. The early lesions of the former group were in the renal parenchyma in the region of the convoluted tubules or in the central portion of the papillae. In ascending infection the primary lesion was in the pelvic lining and peripelvic tissues. The infection could be traced from the bladder through the ureter and periureteral lymphatics.<sup>49</sup> In both cases the infection spread so rapidly after reaching the kidney that it soon became impossible to determine which area was first involved. The infection appeared to spread via the perivascular tissues not by direct extension through the tubules. Cabot and Crabtree<sup>17</sup> also state that lesions of ascending and hematogenous infections are indistinguishable. It should also be stated at this point that hematogenous infection may originate in the kidney pelvis where the first evidences of renal inflammation appear and that ascending infection may exert its chief manifestations in the parenchyma. The point to be emphasized is that the route of infection and its mode of spread is of secondary importance as compared with the existence, location and etiological factors of the primary focus.

*Pathology*.—Kretschmer<sup>37</sup> reported that among 169 cases of pyelitis mostly due to the colon bacillus 120 were bilateral 32 in the left. In the acute stage usually enlarged some appears congested and with yellowish gray lines. The mucosa of the pelvis is usually inflamed and pus may be found in the lumen. In long standing chronic cases the cortex may be thinned or completely absent leaving only a shell. Microscopically there is often evidence of acute inflammation of the tubules while the pyramids may be free. There may be edema and extensive polymorphonuclear and lymphocytic infiltration and areas of necrosis (abscesses) of the interstitial tissue peripelvic areolar tissue and pelvic epithelium. The tubules are often dilated and filled with masses of desquamated epithelium bacteria and pus. Bacilli

are occasionally found in the interstitial tissues. Microscopic abscess formation is usually caused by the confluence of destructive processes involving groups of tubules. Glomeruli are involved only by direct extension of inflammation. Healing when it does occur is rapid and often leaves scar tissue though seldom enough to interfere with normal excretion. In chronic cases most of the kidney substance may be destroyed.

attention to the disease and often dominate the picture throughout. Frequency, urgency, burning or pain on urination, turbid urine and hematuria are common complaints. The manifestations vary greatly. Acute pyelitis or pyelonephritis may be entirely silent as to local symptoms even when severe or may give rise to marked local and general symptoms when relatively mild. Usually but not always

kidney region

stretching of

regions especially on hammer percussion. The kidney may be palpable and tender. The symptoms may suggest acute cholecystitis or appendicitis.

The general symptoms may commence insidiously but usually with a sudden chill and fever. Abdominal distention, anorexia, malaise, chills and sweats are common. Vomiting may occur. The fever curve is often of the remittent type and usually lasts from three to ten days. Herpes simplex commonly occurs.

The infection tends to heal spontaneously unless the causative factors mechanical or infectious remain. Under the latter con-

fever, occasional chills, cachexia and may succumb to exhaustion, secondary infection or may pass into uremia because of loss of

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a tight fitting uterus in an inelastic pelvis and to other causes which interfere with the normal outflow of urine. Infection is commonest in primipara during the fifth to the seventh months of pregnancy. The usual signs and symptoms occur. Relapses are apt to recur in succeeding pregnancies.

The urine contains pus because the colon bacillus affects chiefly the renal pelvis and tubules. The quantity of pus bears no constant relationship to the severity of the process. In rare cases in which the lesions are in the cortex the urine may be clear. Albuminuria

tion. They may be present merely because of reduced resistance induced by infection due to other organisms. The quantity of urine at first is often diminished but may be increased later in the course. The urine in chronic cases may be thick, yellowish green and foul smelling.

*Diagnosis*—Diagnosis rests on many of the points just discussed. Modern urological methods of cystoscopy, ureteral catheterization and roentgenographic studies have simplified diagnosis and frequently permit a diagnosis to be made early in the course of disease.<sup>8</sup> Instrumentation may be harmful in the acute stage. Intravenous pyelography is valuable in certain cases not suited to catheterization.

In many cases the symptoms caused by conditions which were the ultimate cause of the renal infection dominate or obscure the picture. In the typical acute case the bladder symptoms in addition to pain in the lumbar region and the symptoms of general infection point to renal infection. The cystoscope should be used gently and only when definite indications exist for it is impossible even with the best of technique to avoid a certain amount of trauma which so often serves as a portal of entry for colon bacilli into the blood stream. Cystoscopy and ureteral catheterization especially when aided by roentgenographic study are highly valuable in determining the presence or absence of abnormality and whether one or both kidneys are involved. The presence of stones, dilations or narrowing of the calyces, the amount of destruction in the kidney, and the demonstration of the presence of colon bacilli in the urine are all factors which may be demonstrated in the course of the investigation.

ment of the secreting tubules. This often serves to distinguish colon bacillus infection from staphylococcal or other infections affecting chiefly the cortex in which the secretory power is less affected. In acute unilateral colon bacillus infections there is no retention of metabolites in the blood when both kidneys are involved retention may occur.

Beckman<sup>10</sup> demonstrated specific agglutinins in the blood in cases

of colon bacillus pyelonephritis. Bitter and Gundel<sup>14</sup> believed that hemolytic colon bacilli produced severe symptoms of acute disease, while non-hemolytic strains tended to cause lower-grade and chronic infections. Lowenberg<sup>39</sup> found that the hemolytic variety was the most common etiologic agent.

When examining the urine it is absolutely essential to obtain 'clean' specimens. Urine in colon bacillus infections is said to be acid, from staphylococcal infections, alkaline. Pyuria and hematuria are present. In the past, much emphasis was placed on the fact that urine from cases of pyelonephritis when filtered through paper remained cloudy, while urine from cystitis filtered clear. Careful microscopic and cultural studies must be made of the urine of each kidney separately. Care must be exercised not to overlook other organisms, especially tubercle bacilli, even though colon bacilli are present. A sterile urine in pyelonephritis should suggest tuberculosis. Casts containing pus and blood cells occur

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When both kidneys are involved, signs and symptoms of uræmia may develop. Pyelograms show evidence of destruction of the pelvis and cortex.

*Treatment*—Most of the acute cases recover spontaneously if the predisposing factors or foci of infection are eliminated. It is said that in general 50 per cent recover completely, 30 per cent have relapses and 20 per cent become chronic. General treatment,

Chief attention should be devoted to the detection and elimination of contributing factors and foci of infection, many of which are mentioned on page 307.

Very little can be accomplished in the actual treatment of pyelitis or pyelonephritis in itself. Residual bladder urine, in cases of obstruction, should not be permitted to reaccumulate. If, during cystoscopy, no urine can be seen coming from one ureteral orifice, drainage should be reestablished by ureteral catheterization. Release of urine impounded by obstruction of the ureter with pus and debris or other cause often gives striking relief from pain. The

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to further complications instead of relief. Many believe it desirable to alter the reaction of the urine, since colon bacilli grow best

within certain degrees of acidity and alkalinity. The sudden and repeated alteration of the reaction of the urine from acid to alkaline it is said, renders growth conditions for the bacilli unfavorable. Sodium bicarbonate 4 g (30 grains), or potassium or sodium day, for 3 day or two 1

or two of acidity, induced by, acid sodium phosphate, 2 g (30 grains), or ammonium chloride 2 g (30 grains), four times a day or more, until the urine is acid to methyl red, is recommended. Successful results are reported in the treatment of chronic pyelitis, especially in children by the use of a ketogenic diet as suggested by Helmholz. Under this regime, attempts are made to keep the pH of the urine below 5.5 and to attain a concentration of about 1 per cent  $\beta$  hydroxybutyric acid in the urine. Ammonium chloride may be used to assist in the acidification of the urine. The water intake should be restricted during the treatment.

Surgical procedures (decapsulation) as a rule, are not recommended in acute cases. In certain selected instances, however, nephrostomy appears to give striking relief. In chronic cases or under special circumstances in acute cases, when one kidney is involved, nephrectomy should be considered. When nephrectomy is necessary it should not be delayed lest both kidneys become involved.

**Drug Therapy**—Although much has been written on the subject, the reports of benefit derived therefrom are most unconvincing. The long list of drugs recommended attests to this statement. The hope of sterilizing the kidney pelvis with antiseptic lavage is futile. A cursory consideration of the underlying pathology and the penetration of infection deep into the tissues renders such procedures illogical. Even if the infection were superficial, it is doubtful whether the field could be sterilized without destroying the tissue itself. Careful critical studies of some of the newer complex chemical compounds recently recommended have confirmed their efficacy against various bacteria when suspended in plain broth in the test tube, but the addition of small amounts of urine and especially of serum, at once diminishes or destroys bactericidal activity. Similar remarks apply to the use of many substances recommended for intravenous medication. Controlled experiments do not justify their use clinically. Nevertheless further work

purely experimental

**Infections of the Kidney Due to Colon Bacilli and Pyogenic Cocci**—Kidneys in which resistance has been reduced by infection with other

the invasion of pyogenic cocci. These facts probably account for

cultures are secured from various portions of the kidney when sectioned the results are apt to be misleading—for bacilli alone may be found in one area cocci in another and both in a third.<sup>17</sup>

The pathology and symptoms of mixed infections are obviously confused and may be most typical of the infections discussed preceding or of those succeeding this subgroup depending upon the predominance of effects of either one or the other organism.

**Staphylococcal Infection of the Kidney.** This infection gives rise to lesions described as suppurative nephritis kidney abscesses carbuncle of the kidney septic infarct or acute pyonephrosis. It seems simpler however to regard the lesions as cortical infections caused by the staphylococcus differing only in number size distribution degree of coalescence and age. Lesions caused by the staphylococcus often extend toward the surface of the kidney either through the lymphatics or by contiguity pass through the capsule and cause perinephritic abscess. The infection is usually acute but may become subacute or chronic.

The relative incidence of staphylococcal infections of the kidney is shown in Table 29. The frequency of infection is probably dependent upon the frequency with which the staphylococcus invades the blood stream. Various factors render the kidney subject to infection. Males are more frequently affected than females probably because of greater exposure to trauma and skin infections. The lesion is frequently unilateral. In Nesbit's<sup>18</sup> series the right side was affected in 31 cases the left in 12 and both in 5. It seems probable that necropsy studies would reveal a much higher percent

healed. Occasionally no focus can be found and the infection appears to be primary in the kidney. Many cases of staphylococcus infection elsewhere in the body occur in which specific kidney lesions develop but only as a minor factor and are often not recognized clinically.<sup>19</sup> These forms fall into Group II.

*Pathology* — The infected kidney is usually enlarged from congestion and edema. Scattered abscesses may be seen protruding or a single large carbuncle may be present. In the early stages the cut surface may reveal a variable number of abscesses of different sizes scattered throughout the cortex or there may be one large area of suppuration (carbuncle septic infarct). The entire parenchyma is seldom involved. The medulla is seldom seriously affected and the pelvis usually escapes so that unless an abscess ruptures into the pelvis pyuria does not occur. In later stages the abscesses may enlarge and become confluent. They may perforate the cap,

and evolution of the lesions are similar to those caused by staphylococcus elsewhere in the body. The lesions are often found in various stages of development from the earliest inflammation to complete healing. Widespread lesions may heal with almost complete restoration of the normal parenchyma. Occasionally *B. coli* appears as a secondary invader and causes infection which may outlast the original one. Staphylococci may be present in the kidney pelvis without evidence of pyelitis.

*Symptoms* — The symptoms may be chiefly referable to the kidney or may be entirely constitutional with little or no evidence of renal disturbance. In the typical case there is frequently a history of minor infection elsewhere in the body followed by a sudden chill fever pain and tenderness in the costo vertebral angle. The pain is usually of moderate severity and constant but occasionally is of the renal colic type and radiates down the ureters. Cystitis occasionally complicates the infection. Chills and sweating may recur. Otherwise the general symptoms of acute infection are present including anorexia malaise remittent fever and leukocytosis averaging 15 000. Vomiting is uncommon. Initial oliguria may occur.

others claim that only rarely do acute uncomplicated staphylococcus infections become chronic. Perinephritic abscess occurs in perhaps 10 per cent of cases.

The urine may be normal except for traces of albumin common to most infections. Nesbit<sup>28</sup> found staphylococci in the urine at some stage of the disease in each of his 48 cases. Occasionally no growth occurred when samples of certain urine specimens in which staphylococci were seen were cultivated on artificial media. Gross and microscopic hematuria occur in a relatively small percentage of cases. Pus cells are seldom found unless an abscess ruptures

into the pelvis or unless the tubules are invaded or colon bacilli become secondary invaders

Tenderness on hammer percussion may be of value, but it is often present in normal individuals. The kidney may be palpable and tender. The presence of staphylococci in the urine or in the blood stream is strongly suggestive. The identification of staphylococci from pus aspirated with an exploring needle from a swelling in the lumbar region is of great value especially when perirenal suppuration is present. Ureteral catheterization assists in determining whether one or both kidneys are involved if surgical intervention is considered. The phenolsulphonephthalein test is usually normal. The urine is said to be alkaline in reaction. Other conditions such as acute appendicitis, cholecystitis or other abdominal inflammation, may be confusing. Acute hydronephrosis can be detected by ureteral catheterization or by roentgen-ray studies.

*Treatment*—Although general opinion has strongly favored nephrectomy, if the involvement can be proved to be unilateral, it is ordinarily unnecessary. Decapsulation is not recommended. Surgical drainage is usually required for perirenal abscess. In certain chronic complicated cases with unilateral involvement, nephrectomy is necessary. Antiseptics injected into the urinary tract or into the blood stream or given otherwise are useless. The use of specific bacteriophage is as yet unwarranted.

*Tuberculosis of the Kidney*—Tuberculosis of the kidney comprises from 15 to 24 per cent of renal infections found at necropsy. Clinically the percentage is much lower. About 10 per cent of tuberculosis patients examined at necropsy show tuberculous lesions in the kidneys. Meillar<sup>42</sup> found renal tuberculosis in 22 out of 30 cases of advanced tuberculosis. The involvement was bilateral in each case. Wildbolz<sup>47</sup> believes that in the early period only one kidney is affected. Only 12 per cent of his 1000 cases were bilateral. Other observers report bilateral involvement in about 50 per cent of cases.<sup>46</sup> Accurate knowledge on this point would be of great importance considering the benefit frequently obtained in suitable cases by nephrectomy.

Renal infection is usually secondary to active infection elsewhere, in 30 to 50 per cent of cases in the lungs and 15 to 25 per cent in the genitalia. In certain cases, the lesion appears to be primary



in the kidney—at least the dominant cause—of urinary system life. Males are more blood-borne. The possibility of ascending infection is denied by some but not by all.

circumstances suitable for growth in the tissues of the lower urinary tract. The rôle of hypersensitivity in the development of renal tuberculosis is at present uncertain.

There is no selective action of tubercle bacilli for renal tissue. Infection may be the result of constant seeding of bacilli carried by the blood stream from a distant focus and deposited in tissues whose resistance has been reduced by 'toxemia' accompanying the infection. Lodgement and growth of bacilli, hypersensitivity and any of the factors of mechanical interference already mentioned may predispose the kidney to infection. According to Medlar,<sup>16</sup> the first lesions most frequently arise in the glomeruli or tissues between the tubules in the cortex and occasionally in the papillæ or in both localities. The lesions were cortical in 75 per cent of his cases, medullary in 11 per cent and were present in both areas in 13 per cent. Cabot and Crabtree<sup>17</sup> and others found the earliest lesions at the base of the pyramids. Wildbolz<sup>18</sup> found them localized near the papillæ and calyces. Extension to other areas takes place through the interlobular lymphatics and may involve the subcapsular lymphatics (Fig 67, insert a).

As mentioned previously, the significance of the presence of tubercle bacilli in urine has been much debated. A number of competent observers claim that tubercle bacilli may be secreted by a kidney which shows no evidence of tuberculosis pathologically. Others believe that tubercle bacilluria always indicates some degree of kidney involvement no matter how minimal.<sup>19,20</sup> In certain cases of tubercle bacilluria due to one tuberculous kidney, bacilli are occasionally found in urine obtained from the sound side. Their presence there, according to Wildbolz, may be due to reflux up the ureter or to contamination of the catheter during its passage upward. It, therefore, cannot be accepted that the presence of tubercle bacilli in the urine alone is evidence of tuberculosis of the kidney.

*Pathology*—Grossly the kidney may appear normal except when large tubercles appear near the surface. When large caseous areas are present, the kidney may appear lobulated and feel boggy. Less frequently the kidney is uniformly enlarged, due to fibrous or fatty infiltration without cavity formation, or the kidney may be

shrunk with all renal tissue replaced by scar tissue caseous or calcified areas. The perirenal tissues may be involved.

Wildbolz considers three general forms. (a) Nodular or caseo-cavernous characterized by discrete or confluent tubercles of varying sizes distributed throughout the cortex and medulla similar to the specific lesions found elsewhere in the body. In later stages caseation and cavitation are found. Tubercles may involve or rupture into the pelvis causing tuberculous pyelitis. The lesions may be entirely confined to one kidney but when the disease has become chronic both are usually involved one more than the other. The cavities gradually enlarge and coalesce. Ultimately the tuberculous process involves the ureters and bladder. Stricture of the ureter may cause pyonephrosis. (b) In the fibrotic or indurative form caseation does not occur instead the tubercles become encapsulated or fibrotic. (c) In tuberculous nephritis character-

ably partly due to the toxic effects of the soluble substances liberated *in situ*. Similar lesions have been produced experimentally by the injection of tuberculin or of other products of tubercle bacilli. A number of observers however doubt the existence of a tuberculous nephritis. All three forms may give rise to pyuria and bacilluria. Amyloid deposits are often found in the chronic cases. In Wessels' series the pathological changes found at necropsy were grouped as follows: Miliary tuberculosis 115 pyelonephritis 30 pyonephrosis 11 nodular parenchymatous tuberculosis 9 isolated cavitation 8 tuberculous infarcts 5 caseous medullary foci 2.

Histologically the typical tuberculous lesions are like those found elsewhere in the body. Unless the process has progressed to the state of caseation and destruction healing with scar formation may occur just as healing of tuberculous lesions elsewhere in the body may take place.

*Symptoms*—Early tuberculosis of the kidney is most often symptomless for long periods or masked by symptoms of infection elsewhere. Local manifestations arise when abscesses or cavities become large enough to interfere with normal drainage or when secondary infection takes place. Wildbolz proposes the onset be grouped into four classes. (a) Cystitis the commonest early symptom. (b) renal colic with lumbar pain radiating downward with

and stretching of the capsule or to the colic incident to the intermittent blockage of the ureter by the passage of clumps of pus debris or clots. Hematuria gross or microscopic is frequently noted

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may persist for years with remissions and relapses the condition gradually growing worse. General symptoms may be absent for long periods of time but usually there are night sweats loss of

Extensive involvement may  
ral reaction and small lesions  
If untreated the outcome is

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*Diagnosis* All efforts should be made to establish early diagnosis before destruction has advanced too far. Early diagnoses are being made more and more frequently due to increased knowledge and to improvements in urological diagnostic methods. The presence of tuberculosis elsewhere in the body and the appearance

in urine obtained by ureteral catheters by stained smear or cultural methods or by guinea pig inoculation. The problem referred to before in deciding whether a kidney which is excreting tubercle bacilli is tuberculous or not may indeed be difficult. Retrograde pyelography is of distinct value in doubtful cases. In the earliest stage it is

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lesion in the kidney although it is very suggestive. Other tuberculous foci for example in the prostate may shed tubercle bacilli into the urine. It is at present often impossible to distinguish clinically between the various forms of tuberculous involvement of the kidney. Certain differential points have been noted. The secretory function of the kidney as measured by dye tests is more

rapidly reduced in the caseous forms than in so-called tuberculous nephritis. There is often a marked delay and decrease in the excretion of indigo-carmin and of urea. The "toxicity" which occurs during the caseous forms is greater. In the late stages of tuberculous nephritis marked disturbances of function occurs.

*Prognosis*—It is generally recognized that most cases of untreated renal tuberculosis end fatally, often within a year or two. On the

after operation. The remainder succumbed chiefly to tuberculosis of the opposite kidney, to pulmonary or miliary tuberculosis and 15 per cent died from other intercurrent diseases. The immediate mortality among selected cases operated upon was about 25 per cent.

never heal completely.

*Treatment*<sup>18,19</sup>—The ideal subject for nephrectomy is one without active tuberculous infection elsewhere whose general condition is good and in whom tuberculous caseation and cavitation are limited to one kidney. Nephrectomy is contraindicated in definite bilateral infection or during active tuberculosis elsewhere. Careful examination and good judgment are needed. All efforts should be made to determine whether tubercle bacilluria, if present, is due to reflux of infected urine from the bladder, to contaminated catheters and whether the actual process in the kidney is of the type regarded by some as tuberculous nephritis or is actually caseating and destructive. When the destruction is unilateral nephrectomy is indicated. If there is doubt whether the condition is of one or another type the patient should be observed for several months.

*Syphilis of the Kidney*<sup>6</sup>—Syphilitic nephritis has been described by Stoeckenius<sup>22</sup> and Rich.<sup>49</sup> The latter found 13 cases among

surface of the kidney showed glistening flecks often several millimeters in diameter. The cut surface showed grayish-white flecks and streaks replacing the striæ and extending to the medulla. In later stages of healing, large scars caused a roughened appearance of the whole kidney akin to *hepar lobatum*. The process varies greatly in extent. It may be diffuse and destroy large portions of

and stretching of the capsule or to the colic incident to the intermittent blockage of the ureter by the passage of clumps of pus debris or clots. Hematuria gross or microscopic is frequently noted. In later stages there is often a sense of fullness or discomfort in the lumbar region and the kidney may be palpable and tender. Perirenal involvement intensifies the symptoms. The symptoms may persist for years with remissions and relapses the condition gradually growing worse. General symptoms may be absent for long periods of time but usually there are night sweats loss of weight malaise and afternoon fever. Extensive involvement may be accompanied by but slight general reaction and small lesions may cause profound illness. If left untreated the outcome is usually fatal.

*Diagnosis*—All efforts should be made to establish early diagnosis before destruction has advanced too far. Early diagnoses are being made more and more frequently due to increased knowledge and to improvements in urological diagnostic methods<sup>1</sup>. The presence of tuberculosis elsewhere in the body and the appearance of urinary symptoms should cause suspicion. All cases of persistent pyuria especially if the pus is sterile should be suspected as tuberculous. Frequent careful search should be made for tubercle bacilli in urine obtained by ureteral catheters by stained smear or cultural methods or by guinea pig inoculation. The problem referred to before in deciding whether a kidney which is excreting tubercle bacilli is tuberculous or not may indeed be difficult. Retrograde pyelography is of distinct value in doubtful cases. In the earliest stage it may reveal minute areas of destruction at the tips of the papillæ. In late cases large cavities may be evident. Retrograde pyelography is often valuable in determining whether the opposite kidney is sound or not.

The amount of urine excreted may be normal. Polyuria may occur in unilateral disease and oliguria may exist in bilateral involvement. Albuminuria commonly occurs. Pyuria occurs when the pelvis and lower urinary tract becomes infected. Gross or microscopic hematuria is common. Urine from a severely involved kidney may be impounded so that the bladder urine which comes from the sound organ may be normal. Failure to find bacilli does not rule out tuberculosis. In rare cases tubercle bacilluria may be the only abnormality. In early cases the presence of bacilluria with or without pus cells does not necessarily indicate a destructive lesion in the kidney although it is very suggestive. Other tuberculous foci for example in the prostate may shed tubercle bacilli into the urine. It is at present often impossible to distinguish clinically between the various forms of tuberculous involvement of the kidney. Certain differential points have been noted. The secretory function of the kidney as measured by dye tests is more

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*Prognosis*.—It is generally recognized that most cases of untreated renal tuberculosis end fatally, often within a year or two. On the other hand, patients may survive for many years without suffering much disability. Among 270 cases in which nephrectomy had been performed by Wildbolz, about 60 per cent were alive ten years after operation. The remainder succumbed chiefly to tuberculosis of the opposite kidney, to pulmonary or miliary tuberculosis and 15 per cent died from other intercurrent diseases. The immediate mortality among selected cases operated upon was about 2.5 per cent.

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*Prognosis* — It is generally recognized that most cases of untreated renal tuberculosis end fatally, often within a year or two. On the other hand patients may survive for many years without suffering much disability. Among 270 cases in which nephrectomy had been performed by Wildbolz about 60 per cent were alive ten years after operation. The remainder succumbed chiefly to tuberculosis of the opposite kidney, to pulmonary or miliary tuberculosis and 15 per cent died from other intercurrent diseases. The immediate mortality among selected cases operated upon was about 25 per cent. Complete healing and scar formation with more or less diminution of function may occur in the types regarded as tuberculous nephritis or fibrosis. It is probable that caseating and destructive lesions never heal completely.

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surface of the kidney showed glistening flecks often several millimeters in diameter. The cut surface showed grayish white flecks

greatly in extent. It may be diffuse and destroy large portions of







the parenchyma. The tubules may be primarily or secondarily involved by pressure of the newly formed granulomata. Microscopically, typically granulomatous syphilitic lesions are present although Rich was unable to detect spirochetes. Warthin showed that the interstitial tissue is primarily attacked by the spirochetes which then pass through the walls of the tubules into the lumina. The glomeruli are not primarily damaged.

Diffuse or conglomerate gummata or diffuse syphilitic patches have been occasionally noted in the cortical region usually affecting one kidney. Evidence of large gummata can sometimes be visualized by pyelography. The histology is typical of syphilitic lesions found elsewhere. Congenital syphilis is manifested chiefly by microscopic changes; gummata are rare.

*Symptoms*—When clinical or laboratory evidence of nephritis appears during syphilis it is necessary to suspect its specific origin. The kidneys may presumably be damaged by the excretion of injurious substances elaborated by the infection at a distance or locally. When the kidney tissue has been largely destroyed by the specific process the signs and symptoms of uremia occur. It has been suggested that active antisyphilitic treatment in itself may damage the kidney and it is therefore sometimes withheld when evidence of renal impairment is found. Knowing the possibilities of actual specific infection and the unlikelihood of kidney damage resulting from proper therapy, antisyphilitic treatment should be continued in spite of evidence of kidney disease. Indeed evidence of nephritis or nephrosis often disappears under active therapy.

**Gonococcus Infection of the Kidney** Gonococcus infection of the kidney is a rare occurrence. Reports of 28 cases have been collected by Johnson and Hill.<sup>22</sup> The organism was positively

found in 15 of these cases. Morphologists believe it ascends from the primary urethral lesions by the backflow of urine through the lymphatics or by inflammation migrating along the ureters. Many cases are complicated by urethral or ureteral strictures and hydro-nephrosis or pyonephrosis. In many cases colon bacilli or other organisms appear as secondary invaders. In the typical case the lesion consists of intense follicular inflammation in the pelvis. Distinct abscesses may occur.<sup>23</sup> Destruction of the parenchyma and pyonephrosis often result from chronic obstruction.

Clinically the symptoms may resemble those of tuberculosis but usually are uncharacteristic and depend upon the situation, extent and severity of the lesions and the degree of obstruction or destruction present. Clinical diagnosis is often presumptive and suspected from the history or presence of urethral gonorrhea or by the presence

of gonococci and pus in the urine obtained by ureteral catheterization. The blood culture may be positive in severe acute cases. The prognosis is unfavorable. Endocarditis or other metastatic infections may occur.

*Treatment* — The treatment is usually symptomatic. The primary forms should be eradicated. Nephrectomy is indicated in chronic forms with unilateral involvement and destruction.

*Actinomycosis* — Actinomycosis is an uncommon disease in general and rarer still as a "primary" infection of the kidney. Obviously the portal of entry or primary focus must exist elsewhere in the body, in the skin, the lungs, the intestinal tract or elsewhere. When the primary focus is located in the skin, for example, and recognized as actinomycosis, diagnosis of invasion of the kidney is simplified. In certain rare instances, however, the chief manifestations occur in the kidney. Reports of such cases are few and unilateral involvement is the rule.

The disease is characterized by slowly developing anemia, cachexia and eventual death. The infection may burrow and penetrate into the abdominal cavity or externally. Metastatic infections often develop elsewhere and render diagnosis possible during life. The chief clinical features are localized pain, low-grade fever, anemia, cachexia, muscle rigidity anteriorly or posteriorly over the kidney region and a palpable mass which may or may not be tender. The sudden appearance of acute symptoms in the course of the illness may indicate superimposed infection by other organisms or the rupture of an abscess into the pelvis or through the renal capsule. Except when the pelvis is involved the urine is normal or perhaps contains a few red blood cells. Renal function of the involved kidney is unimpaired in the early stages. In the advanced cases the kidney may be destroyed. The perirenal tissue may be invaded, producing the "woody" sense of hardness of the abdominal wall or lumbar region, said to be characteristic of the disease.

The disease is usually fatal within a few months. The prognosis is poor. The only hope of cure is by early removal of the kidney.

in long-standing cases.

*Diagnosis* — Unless the disease is in mind, cases are most frequently regarded as tuberculosis or tumor of the kidney because of the clinical signs, symptoms and chronicity. Pyelograms may show evidence of destruction or of compression of the pelvis. When an abscess ruptures into the pelvis, the process is apt to be regarded

as suppurative pyelitis. The urine should be carefully and repeatedly examined for the fungus. Acid fast rods must be differentiated from tubercle bacilli by guinea pig inoculation or by culture on artificial media. The diagnosis becomes evident when the typical granules are found in the urine in pus from metastatic lesions in accessible parts of the body from pus aspirated from the local lesion or in tissue removed at biopsy and examined histologically and bacteriologically. The organisms can be cultivated in artificial media or injected into experimental animals for further identification.

*Prognosis* Unless the process is actually localized in one kidney and removed by nephrectomy the disease is invariably fatal in several months or years.

*Treatment* — The treatment resolves itself to surgical removal of the infected tissue if the process does not exist elsewhere as well. Drug therapy is without specific value.

**Echinococcus Cyst or Hydatid Disease** — *Echinococcus* cyst or hydatid disease of the kidney<sup>21</sup> like the preceding infection is rare. Kretschmer in 1923 collected 18 cases reported in North America and several have since been added. The *Echinococcus granulosus* is a minute tapeworm infesting chiefly the dog's intestine. Its eggs are shed in the feces and find their way to the intestinal tract of man. The eggs hatch, enter the portal circulation and usually lodge in the liver. They may pass this barrier and come to rest in other organs in the kidney for example in about 2 per cent of cases. Once located they develop into unilocular cysts filled with serous or gelatinous fluid and become surrounded by a tough fibrous wall. The inner germinal layer produces buds or daughter cysts which may remain attached or float free in the fluid. Rupture of the cyst liberates the daughter cysts each of which is capable of producing another large cyst.

The disease is almost always unilateral and usually a single cyst is present. In the early stage the cyst merely acts as a foreign body simulating a tumor. It may reach the size of a football and destroy the kidney by pressure. The symptoms and signs are those of renal tumor. There is often a sense of fulness or uneasiness in the lumbar region and a mass may be seen or felt. The general health may be unaffected. Hematuria may be present. Secondary infection or rupture of a cyst into the pelvis may be followed by symptoms of cystitis or pyelonephritis. The course of the disease may be punctuated by attacks of pain caused by the passage or

<sup>21</sup> not in the refer

discharge of the cyst contents. Usually it results in death by exhaustion by extension to other organs or by intercurrent infection.

When the diagnosis is in doubt, a careful urological studies were able to diagnose 1 of 3 cases before operation. Diagnosis is easy when the cyst is aspirated or ruptures spontaneously and daughter cysts or hooklets are found in the aspirated fluid or in the urine or when cysts appear in other parts of the body. Pyelography may reveal compression of the pelvis but may show nothing abnormal. Calcified hydatid cysts can be visualized by the roentgenograph. Eosinophilia occurs in 50 per cent of cases. The test of Casoni (the intradermal injection of 0.2 cc of pooled sterile fresh hydatid cyst fluid produces an urticarial wheal in infected individuals) is of value in diagnosis. The complement fixation test of Ghedini is also used.

**Treatment.** The treatment is surgical. Marsupialization is recommended. Conservative operation is justified in localized cysts, nephrectomy when the diagnosis is in doubt or when the cyst has perforated the renal pelvis. Prophylaxis against infection in infested regions should be practised.

**GROUP II — Infections of the Kidney With Chief Manifestations of Disease Elsewhere.** The infections discussed in Group I fall into Group II when the symptoms, signs and pathology of the kidney disease are overshadowed by the manifestations of the infection at the original site of entry, in other metastatic lesions or by generalized disease. In many of the entities discussed in Group II, however, involvement of the kidneys is always of minor importance and seldom gives rise to evidence of clinical disease. When clinical symptoms and signs appear, they depend upon the parts of the kidney most involved and on the extent of the process. These lesions are usually bilateral and heal when the original infection disappears or are recognized only at necropsy. Usually no treatment is necessary. When active intervention is required, it is the

to the excretion of toxic products elaborated during the infection by the plugging of capillaries with unusually large numbers of bacteria and the formation of minute emboli and infarcts when unusually virulent bacteria are concerned or by other factors. It is sometimes impossible to determine whether renal lesions are due to remote effects of an infection elsewhere in the body or to the immediate action of pathogenic organisms locally in the kidney tissues or to a combination of both factors.

**The Bacillary Infections**—The *colon bacillus* heads the list and is discussed more fully on page 307. During *colon bacillus* septicemia or involvement of other organs or tissues the kidney may be mildly affected and play a minor rôle in the production of symptoms or may be entirely unaffected. *B. proteus* infections<sup>40</sup> occasionally occur especially following instrumentation or operation on the urethra or bladder. Septicemia has been observed in 17 cases of which 5 died. During typhoid fever *B. typhosus* may produce multiple abscesses in the renal cortex and medulla. Symptomless bacilluria is common. If obstruction occurs pyonephrosis results. Both kidneys are usually involved. Numerous reports have been gathered by Patch<sup>45</sup> who adds 2 cases of his own. Christeller<sup>13</sup> regards the lesions as typical. Typhus Knotchen. *Tubercle bacillus* infection of the kidney is discussed on page 315. Gregerson and Lund<sup>27</sup> and Wohlwill<sup>19</sup> found microscopic areas of specific granulation tissue and inflammation in the kidneys due to *Brucella melitensis* during undulant fever. Several cases of pyelonephritis due to *B. dysenteriae* are reported by Calalb<sup>15, 40a</sup>. Jean<sup>23</sup> records a case of anthrax of the kidney with perinephritic abscess. Because of the massive bacteremia which occasionally occurs in anthrax the kidney capillaries contain myriads of bacilli which may produce lesions by mechanical obstruction alone. The specific lesions of glanders<sup>13</sup> frequently occur in the kidney during the infection. Schottmüller<sup>13</sup> reports 2 cases of *gas bacillus* infection in which many of the renal vessels especially in the glomeruli were plugged with bacilli. The tubules were filled with debris and bacilli were found in the urine. Metastatic lesions may occur in the kidneys during plague<sup>13</sup> and probably in tularemia. Miller and Branch described infarcts in the

cystes around many gl

kidneys are commonly

invasion of the vibrios

in the kidneys. In leprosy<sup>13</sup> the kidneys in rare cases are infiltrated with leprous nodes and tissue. Myriads of bacilli may be present and escape into the urine.

**The Coccal Infections**—The *staphylococcus* because of the frequency with which it invades the blood stream is the commonest encountered. The kidney is the chief site involved in certain cases as described on page 313. Frequently it is one of many organs or sites involved in widespread metastatic invasions. Joyce<sup>25</sup> states that of 61 cases of staphylococcal infection renal lesions occurred in 14. Because of the cortical location of the abscesses there may be little or no evidence of

found only at necropsy

hemolyticus are of two

kidney by the toxic products of growth which give rise to bio

nephritis, described at length in Chapter XXI, and (b) by direct invasion of renal tissue and abscess formation. Seven cases of streptococcus infection of the kidney are described by Cabot and Crabtree.<sup>17</sup> The kidneys were often enlarged. Abscesses were usually multiple and were present in varying stages of development. They were found scattered in the cortex and medulla. Thrombi containing chains of cocci were found in various portions, often

There was a focal reaction in the cortex and medulla, but no definite bacterial emboli were found after twenty four hours. Cocci appeared in the urine. Strang and Semsroth<sup>18</sup> report acute endarteritis and destruction of the intima of the renal arterioles probably caused by *Streptococcus viridans* septicemia. In subacute bacterial endocarditis associated with *Streptococcus viridans* bacteriemia,<sup>19</sup> diffuse glomerulitis, embolic and focal glomerulitis occur in a high percentage of cases. Streptococci lodge in the capillaries and cause hyaline and fibrous changes. Bell<sup>20</sup> believes that necrosis of the glomeruli is probably a toxic effect rather than the result of infarction. Clawson injected streptococci into the blood stream and noted that inflammatory lesions of low intensity developed about the masses of cocci which were deposited in the kidney. The importance of infected teeth and tonsils as foci of infection of streptococcus *viridans* infection has been greatly exaggerated. Lesions produced by the gonococcus have been discussed on page 320. The pneumococcus, like the hemolytic streptococcus, may affect the kidneys in different ways: first as a result of the excretion of toxic

meningitis, multiple kidney abscesses and perinephritic abscess due to pneumococcus Type III.

The kidneys were enlarged and boggy. The surfaces were irregular, due to the bulging of numerous abscesses. On section, innumerable

were necrotic and contained polymorphonuclear leukocytes. They were surrounded by a zone of inflammation. Focal and diffuse areas of leuko-



varying degrees of degeneration. During the illness no abnormalities of the urine other than those found in acute infection were present.

Castaigne reported a case of renal abscess due to *M. tetragenus*.

**The Filtrable Virus Infections**—Hemorrhagic nephritis may occur as a result of direct action of the virus of *varicella*. In *smallpox* Weigert found small foci of specific lesions in the kidney. Iahr reported small round cell infiltrations in *measles*. In *yellow fever* engorged glomeruli, dilated tubules, hyaline and granular degenera-

rhages in the pelvis and intranuclear inclusion bodies in the cells of the tubules in 50 per cent of cases at necropsy. The urine during life occasionally contained albumin, pus, erythrocytes and casts. The non-protein nitrogen of the blood was occasionally increased. It is uncertain whether the changes found were associated with encephalitis or were merely secondary in nature.

**The Spirochete Infections**—Syphilis of the kidney is discussed on page 319. The kidneys are frequently affected in *relapsing fever*. Masses of spirochetes may be found in the renal vessels. *Heil's disease* (infectious jaundice) almost always affects the kidneys. They are often doubled in size and show hemorrhages, inflammation and cellular infiltration.

eterized urine. Other cases are reported by Fischer and filaria embryos may abound in the kidney cortex and medulla. Marked fibrosis and parenchymal degeneration occurs. *Echino-*

produce typical colonies and granulomatous changes. *Blastomycosis*, *streptothricosis*, *sporotrichosis* have been discussed. *Aspergillus* and *actinomyces* may occasionally involve the kidneys. *Actinomyces* are found in the kidney. The lesions of each



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## CHAPTER XXI

### INFECTION BY STREPTOCOCCI IN RELATION TO RECOVERY AND PROGRESS IN NEPHRITIS \*

By WARFIELD T LONGCOPE M D JAMES BORDLEY III M D

AND

FRANCIS D W LUKE'S M D

**Introduction** *Previous Evidence of Hemolytic Streptococci as a Factor in the Etiology of Glomerular Nephritis*—It is now recognized that the onset of acute glomerular or hemorrhagic nephritis is usually preceded or accompanied by an acute infection (Loehlein<sup>1</sup> Fahr<sup>16</sup> Volhard<sup>53</sup> Bell Clawson and Hartzell<sup>6</sup> Kollert<sup>28</sup> Fishberg<sup>17</sup> Munk<sup>42</sup> Gray<sup>9</sup> Lichtwitz<sup>29</sup> Longcope<sup>24,35</sup> Van Slyke<sup>32</sup> Addis<sup>1,14</sup>) Scarlatina tonsillitis severe pharyngitis sinusitis and bronchitis are the forms of infection which are most frequently observed. It is well known too that these infections are frequently caused by hemolytic streptococci and therefore the view has been widely adopted that hemolytic streptococci are intimately connected with the onset of the

course of acute or subacute glomerular nephritis serve to uphold this idea.

Bacteriological studies have now been made of the infections found in 87 of 92 cases of acute or subacute glomerular nephritis.† In all but 3 cases some definite infection usually of the upper respiratory tract was obvious. Cultures made from the infections in 11 of these 87 patients did not show an organism that could be held responsible for the infection. Satisfactory information could be obtained however concerning the infecting organism in a total of 76 cases. In 72 of these the infection was associated with hemolytic streptococci of some type. In 6 of the 72 cases there was in addition an infection caused by some other bacteria. A cystitis due to gonococci occurred in 2 of these. lobar pneumonia

\* Aided by a grant from the Ella Sachs Plotz Foundation

† Since this paper has been written a number of additional cases have been observed. Except in a few particulars the studies that have been made on these new cases confirm the observations recorded in this paper.

due to pneumococcus Type II occurred in 2, a sinusitis due to pneumococcus Group IV in 1 case. It was presumed that the infections in 66 cases were caused exclusively by hemolytic streptococci.

Of the remaining 4 patients from whom hemolytic streptococci were not cultured, 1 had scarlatina, 1 suffered from a sinus infection due to pneumococcus Group IV and 2 had bacterial endocarditis due to *Streptococcus viridans*. It is interesting to note that rheumatic endocarditis, causing mitral stenosis and insufficiency, was present in five of the 76 cases.\*

Bacteriological examinations such as this furnish, perhaps, only indirect evidence that hemolytic streptococci are related etiologically to glomerular nephritis. There is, however, considerable corroborative evidence which might support this idea. There seems to be little question for instance that diffuse glomerular nephritis as well as the so-called focal form of the disease, may occur as a complication of bacterial endocarditis caused by *Streptococcus viridans*. Two such cases quite typical in their pathological character were observed in this series while Baehr and Lande<sup>7</sup> state that diffuse glomerular nephritis was noted in 11.5 per cent of their series of 77 cases of bacterial endocarditis. Furthermore, it has been shown that the skin of a large proportion of patients suffering from acute and subacute glomerular nephritis is much more sensitive than is the normal skin to culture filtrates of hemolytic streptococci of  $\beta$  type (Longcope<sup>11</sup>) or to the proteins derived from these organisms (Derrick and Fulton<sup>12</sup>). We have also found that the serum of these patients will agglutinate killed cultures of a limited number of strains of hemolytic streptococci of  $\beta$  type (care was taken to kill the organisms by heat before the agglutination reactions were performed, in order to obviate confusion with the interesting, non-specific agglutination of living cultures of hemolytic streptococci, described by Tillett and Abernethy<sup>10</sup>). Lawson and Wetherby<sup>13</sup> have stated that they could demonstrate agglutination of streptococci with high dilutions of serum from cases of acute nephritis, while Seegal, Heidelberger and Jost<sup>14</sup> refer to the fact that the serum from cases of acute nephritis causes precipitation of the nucleoprotein from hemolytic streptococci of  $\beta$  type.

In the last three years a number of observations have been made

by Dr Allan and one of the authors (W T L) upon the antistreptolysin content of the serum in cases of nephritis during the acute and chronic stage of the disease. In a number of instances the antistreptolysin content of the serum is greatly elevated during the acute stage of the disease and in a few it is found to be high during the subacute stage of the disease. The observations have not yet progressed far enough to show whether the antistreptolysin content of the serum bears any relation either to the course of the infection by hemolytic streptococci or to the course of the nephritis. Such observations as those cited suggest that during the acute and subacute phases of glomerular nephritis the patient may respond abnormally in several ways to hemolytic streptococci or to the proteins of this organism.

There is now in addition experimental evidence to indicate that both hemolytic and non hemolytic streptococci may cause under certain conditions a diffuse glomerulitis in rabbits. The histological lesions produced in this manner imitate very closely the pathological picture of glomerular nephritis in man. A discussion of the literature upon experimental glomerular nephritis and descriptions of experiments may be found in a previous communication (Lukens and Longcope<sup>36</sup>) and in an article by McLeod and Finney.<sup>40</sup> In the first series of experiments killed cultures of hemolytic streptococci of  $\beta$  type were injected into the left renal artery of a series of normal rabbits and of a series of rabbits sensitized to hemolytic streptococci of  $\beta$  type. Diffuse glomerulitis occurred in only 2.5 per cent of the normal rabbits subjected to intra-arterial injections of hemolytic streptococci but in 73.9 per cent of the sensitized rabbits. It was therefore concluded that sensitization or infection of the animal rendered the kidney in some way particularly susceptible to the action of the dead bodies of the hemolytic streptococci which were brought into direct contact with the glomerular capillaries. McLeod and Finney have varied these experiments by using killed cultures of *Streptococcus viridans*. They have found that suspensions of these bacteria in salt solution injected into the left renal artery also cause at times the most

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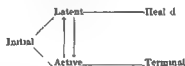
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sensitized animals between the intensity of the skin reaction, the presence of eye reactions and the occurrence of glomerulitis. Lukens<sup>37</sup> was able to produce somewhat similar lesions in the kidneys of a limited number of normal rabbits by making the injections

of killed hemolytic streptococci into the left renal artery of the same rabbit at weekly intervals. It seems therefore to be definitely established that a form of acute glomerulitis, reproducing closely the histological picture of acute glomerular nephritis in man can be obtained experimentally in rabbits. The exact mechanism that is responsible for the inception of this glomerulitis is not, at the present time clear.

Although it is possible that bacteria other than streptococci such as pneumococci may be responsible for the onset of acute

importance to establish beyond the shadow of a doubt the etiology of glomerular nephritis but it is also necessary to understand more precisely the conditions under which the disease is initiated, the method of recovery and the reasons for progression to a chronic stage or to a fatal termination. The elaborate and exact studies of Volhard, of Van Slyke and his collaborators and of Addis have shed much light on the natural history of the disease. The diagram which Addis uses to indicate the various stages of the disease is shown below.



The method too which he has devised<sup>2</sup> for obtaining quantitative estimations of the amounts of albumin and formed elements excreted in the concentrated urine over a period of twelve hours has proved of much value. The method has been employed in many cases which will be presented later. The urea-clearance test devised by Van Slyke etc. has been of much value in estimating the degree of impairment of renal function.

The clinical course of hemorrhagic Bright's disease is varied. During its progress the dominant features of the illness may change in such a remarkable manner that from superficial examination the different stages may seem to bear few resemblances one to another. The complete picture must usually be pieced together from information obtained from observation made over comparatively short periods of the patient's illness. It is the initial or acute phases and the terminal stages that are most familiar. Less is known about the intermediate stages of the disease though the important clinical descriptions of Volhard, Addis and Van Slyke have done much to elucidate this phase and thus bridge the gap.

It is now recognized that the familiar acute or initial stage may be



glomerular nephritis. It is seen most frequently during the course of an acute infection. In all probability the instances of benign

that, in some instances, the symptomless initial stage may progress to a latent phase, and later to the typical chronic form of glomerular nephritis. In occasional instances the amounts of albumin, of red blood cells and of casts, which are found in the urine of these patients with an insidious onset, but without other symptoms or signs, are in all respects the same as those found in patients with an acute onset attended by the marked hypertension, anasarca, nausea and vomiting characteristic of the onset of severe acute hemorrhagic nephritis. Indeed, there is less and less tendency to attempt to distinguish, on clinical grounds alone, a focal form of glomerular nephritis. Addis takes this point of view, and the authors have finally found it impossible to differentiate from clinical examination the two varieties of glomerular nephritis. Therefore, they have included for practical purposes, those patients with extremely mild onset as well as those with violent onset in this series of cases of acute hemorrhagic Bright's disease. The authors have not, however, included a number of patients in this series who, incidental or during the course of rheumatic fever, have shown only focal glomerular nephritis, as has been pointed out by Lynn and by Little, and not unusual.

nephritis such as those recorded by Joeb,<sup>11</sup> by Goldring<sup>12</sup> and by Coburn,<sup>13</sup> have not been encountered by us during the acute stages of rheumatic fever.

Following the acute, or initial stage, the disease may progress, as is well known, in a variety of ways. Rapid and complete recovery may ensue, or the patient may become symptomless and the renal functions normal, but for weeks or months there may be albumin, casts or red blood cells in the urine. This latent phase may end in recovery, change later to an active or, as Volhard designates it, a nephrotic stage, or may progress without this variation in symptoms, after months or years, to the terminal phase. In many

instances the initial stage runs imperceptibly into the active nephrotic or subacute phase. After weeks or months the active stage may be replaced by a latent phase resulting occasionally in recovery but more often terminating fatally. A few patients die in the acute attack. Others progress rapidly from the initial to the active stage and die within a few weeks or months with massive edema, hypertension and hematuria.

It can readily be appreciated from this brief outline that hemorrhagic Bright's disease may pursue an extremely varied course. Unrecognizable at one time except by careful examination of the urine simulating closely in some patients a nephrosis it reproduces in others particularly in the terminal stages a clinical picture of vascular nephritis or nephrosclerosis. It is only when one has followed the entire course of the disease from beginning to end that one can gain an accurate conception of the natural history of glomerular nephritis.

**Plan of the Present Experiments** —Although much has been done to clarify this important part of the problem there still remains considerable uncertainty regarding the factors that are responsible for recovery or which determine an unfavorable progress. In an effort to shed some light on this important matter the authors have followed with considerable care a total of 72 cases of hemorrhagic nephritis. The disease developed in 7 instances under

in a few instances whether the disease was in the late period of the initial stage or in the early period of the active phase. It is possible that 1 or 2 patients were in the latent stage when they were first seen. Observations have been made continuously or at intervals of a few months in this series of 72 patients for periods varying from one to nine years or until the death of the patient. Patients who have recovered completely have subsequently been examined at intervals of six months to one year. In addition to the clinical examinations with cultures from the pharynx determinations of the renal function have been made by the estimation of the phthalein excretion by determining the concentration and dilution of the urine by the non protein nitrogen of the blood and in a few cases by the creatinine

grouped according to the classification of Aldis into those who have recovered those who are presumably in the latent stage those who are in the active or terminal stage and those who have died. Twenty six patients have recovered 7 of these have been followed

for from seven to nine years 4 from five to seven years 5 from three to five years 7 from one to three years and 3 for less than one year.

studied for from five to eight years 5 from two to five years and 2 from one to two years. Twenty two patients have died. In 3 of these patients the disease lasted for from three to five years in 4 from one to three years in 5 from six months to one year in 7 for less than six months and in 3 for less than two weeks. The fatal cases included two examples of subacute bacterial endocarditis due to *Streptococcus viridans* and 3 patients who died during the first two weeks of their illness. One of them had an extensive infection of the throat and cervical lymph nodes due to hemolytic streptococci associated with pneumonia. 1 patient had erysipelas and 1 patient suffered from pansinusitis caused by hemolytic streptococci.

**Factors Determining Outcome of the Initial Attack** — (a) *Severity of the Attack.* — Continuous study of many patients from the initial stage to recovery or through the protean manifestations of the disease to death indicates that there may be several factors which have bearing on the outcome of the disease. It is questionable as to whether the actual severity of the acute attack plays an important part in the eventual recovery, for in some patients who recover completely the acute phase is characterized by severe symptoms with considerable edema, hypertension, oliguria, marked hematuria and albuminuria and a measurable impairment of renal function while in others, who progress to the latent, active or terminal stages of the disease the symptoms at onset are mild, the initial edema is insignificant and the renal functional tests practically within normal limits. The hematuria may be slight but usually the albuminuria is marked.

Though the severity of the acute attack of nephritis in the initial stage of the disease does not seem to be of paramount importance

reaction to the acute infection was sharp with a rise in temperature and with evidence of intoxication though the acute attack of nephritis might be alarmingly severe, convalescence was often rapid and recovery quite prompt. In a careful analysis of these cases they have found that a very large proportion of cases of nephritis which eventually have recovered completely were ushered in by

an infection with severe constitutional symptoms. On the other hand, most of the cases which progressed to a chronic stage, and often resulted in death, were associated with mild chronic streptococcus infections which usually affected the tonsils or the paranasal sinuses. In these patients, constitutional symptoms from the infection were mild and sometimes the infection could not have been discovered unless careful examinations of the sinuses had been made.

(b) **Duration of the Acute Attack**—The prolongation of the acute phase, with persistence of edema and the continuation of marked albuminuria, also seems to influence the eventual outcome. When these features of the disease continue without abatement, or recur during the period of expected convalescence, progress to the active stage is common, and the probability of recovery much reduced. It may be seen from Table 30 that all but 2 of the patients that recov-

TABLE 30—DURATION OF SYMPTOMS BEFORE OBSERVATION

Condition	Total cases	Under 1 month	1 to 6 months	Over 6 months
Well	20	24	2	
Latent	14	10	3	1
Active	10	6	3	1
Dead	23	6	13	3
Total	72	46	21	5

ered came under observation during the first weeks of the disease,

determine with accuracy the termination of the acute or initial stage, but an effort has been made to do this for the patients who have recov-

estimate the duration of the acute phase. Table 31 shows, however,

TABLE 31—DURATION OF INITIAL STAGE OR ACUTE ILLNESS

Condition	Total cases	Under 1 month	1 to 3 months	3 to 6 months
Well	26	11	14	4
Latent	11	1	8	5
Active	6	0	2	4

that in those patients who have recovered, convalescence was almost uniformly established within three months from the onset of the disease, and in about one-half of them this took place within one month. On the other hand, in only 1 of the 14 patients who are now in the latent stage was convalescence established within one month, and in 5, convalescence was not established within three

months of onset. In most of the 6 patients now in the active stage of the disease in whom some rough estimate could be made of the duration of acute symptoms there was no amelioration of these symptoms before at least three months had elapsed.

(c) *Persistence of Infection*—A matter which seems to influence directly the favorable or unfavorable outcome of the acute attack is the persistence of infections. In previous communications evidence was presented to show that the progress of acute or subacute nephritis is quite closely connected with the disappearance or persistence of the primary infection or of the bacteria responsible for the infection. This suggestion is reasonable if it can be demonstrated that the onset of the acute nephritis is directly connected with the primary infection. Under these circumstances it might follow that elimination of the infection or of the infecting organisms would remove the focus which elaborated continuously or intermittently some substance injurious to the kidney. On the other hand persistence of the infection or of the infecting organism might result in progression of the nephritis to a chronic state or to death.

(d) *Relation of Recurring Infections to the Progress of the Disease*—Though there is general agreement that acute infections usually  
have a tendency

infection or through its elimination. Clausen<sup>1</sup> has noticed that the symptoms of the acute nephritis are prolonged by persistence of the infection. Only 1 of his 20 children in whom recovery or rapid improvement occurred within four weeks of onset showed persistence of the primary infection whereas 33 of the 43 cases in whom the symptoms continued for from four weeks to two years had chronic infections. Lytle and Rosenberg<sup>18</sup> also comment on the persistence of infections in their patients who progressed to a chronic stage of the disease. Platt<sup>14</sup> concludes that the course of acute nephritis is favorably influenced by the removal of foci of infection while Gray<sup>9</sup> in a study of acute subacute and chronic glomerular nephritis suggests that the progress from the acute to the chronic state depends upon the persistence of an infection. Guild<sup>22</sup> on the other hand could not determine that the persistence or exacerbation of infections influenced unfavorably the eventual outcome of acute attacks of nephritis which occurred in 34 children. Her examinations were made in 18 cases after an interval of less than five years and in 16 cases after an interval of five years or more. Volhard as well as Van Slyke questions the importance that can be attributed to the persistence or exacerbation of infections in prolonging the course of the acute attack of nephritis or in influencing its outcome. Both Van Slyke and

Addis however recognize the frequency of exacerbation of symptoms during the initial stages of nephritis, following operative procedures or recurrences of infection, but Addis has so rarely

effort was made to eliminate the infections about the throat and paranasal sinuses. Tonsillectomy was performed in many cases, while a few patients were subjected to radical sinus operations. During the repeated observations which have been made on these patients over a period of from one to nine years, cultures have been obtained at fairly frequent intervals either from the persistent infection or from the region which was the seat of the original infection. This latter procedure has proved to be of importance, for in several instances it was found that the responsible organism has persisted in the course of

cases in an attempt to combat the infection.

One point which adds weight to the idea that the activity of the infection influences the renal lesion is the frequent but often fleeting exacerbation of the nephritis following surgical interference with the infection during the initial stage of the disease or in the course of convalescence. This has occurred repeatedly in the authors' experience as it has in the experience of others. The authors have not considered however, that serious or permanent harm has resulted from these transient exacerbations. On the other hand it has appeared that natural recrudescences of the infection by streptococci have been directly related particularly during the initial stage of the disease, to more severe and prolonged exacerbations of the acute symptoms which have had a deleterious effect

week to week and unless the exacerbation of the infection attracts particular attention and the increase in symptoms of the nephritis is severe it is difficult to convince oneself that there is any connection between the two. One rarely can detect as Addis has pointed out a pronounced increase of symptoms during the latent stage

when exacerbations of infections occur. The experience of the authors has been the same when the patient is in the terminal stage of the disease. An exact analysis of the data now available on the relation of infections to the progress of hemorrhagic nephritis in a much larger series of cases than was originally described will shortly be published by McLeod, Winkenwerder and Baker but in the meantime some reference can be made to the results of their studies.

(e) **Latent Period Between Infection and Onset of Nephritis —**

It has been interesting to observe the latent period between the onset of acute streptococcus infection and the onset of the acute nephritis. This as has been generally recognized covers a period of from one to three weeks. Osman, Close and Carter<sup>40</sup> quote Goodall and Turner who state that the appearance of nephritis following scarlet fever comes mainly between the eleventh and thirty-fifth days after the onset of scarlet fever with a maximum incidence about the twentieth day. Osman, Close and Carter however think that the interval between the attack of streptococcal tonsillitis and the onset of acute nephritis is much shorter than it is in scarlet fever. The mean time of onset in 37 post tonsillitis cases was ten days. The statistics which Winkenwerder, McLeod and Baker<sup>41</sup> have collected show that the time of onset following streptococcal tonsillitis or acute streptococcal infection of the upper respiratory tract compares very well with the figures of Osman, Close and Carter. In the 41 cases recorded by Winkenwerder, McLeod and Baker<sup>41</sup> the onset of the acute nephritis appeared on the third to the twenty-eighth day, the average interval being eleven days. It has been interesting to find however that the onset of the acute exacerbation in nephritis following tonsillectomy or the flare-up of a streptococcus infection is much shorter than this. Gross hematuria and marked albuminuria may occur within twenty-four hours after the rise in temperature associated with the flare-up of an infection. Following tonsillectomy or after a radical operation on the sinuses a noticeable increase in blood albumin and casts in the urine has been observed within six to eight hours of the operation. In the serious exacerbations of nephritis edema of the face and rise in blood pressure may be observed within twenty-four hours after the onset of infection or following operation.

Infections by  $\beta$  hemolytic streptococci in patients who have recovered completely from acute nephritis have not on the other hand been attended by recurrence of the signs or symptoms of nephritis. Several of our patients who have recovered have subsequently experienced severe infections of some sort due to hemolytic streptococci and during the course of this illness there has been no evidence of an exacerbation of chronic or latent nephritis and no indication of the onset of a second attack of acute nephritis.

Although sufficient data have not yet been collected from which one could draw conclusions such experiences suggest that the patient who has once recovered from an attack of acute hemorrhagic nephritis is no longer susceptible to a recurrence of the disease when he contracts an infection due to hemolytic streptococci. Patients who have recovered from hemorrhagic nephritis may also become pregnant and proceed normally to term without the recurrence of any of the symptoms or signs of nephritis. This has occurred in 3 of the authors' patients.

As one studies the progress of the disease in these patients with hemorrhagic nephritis from the onset to recovery or death and as one follows the course of the infections in these patients one is impressed with the close relationship which one process bears to the other. In the final analysis one is forced to the conclusion that glomerular or hemorrhagic nephritis is actually one form of an infectious disease. This is its essential character. In certain respects it is analogous to rheumatic fever. If one substitutes the kidney for the heart the two diseases have much in common. The initial stage presents all the characteristics of an acute infection. Sometimes it is in extremely mild form but usually it is of varying degrees of severity. Complete recovery from the acute attack does not seem to leave the patient liable as does an acute attack of rheumatic heart disease to subsequent attacks of the disease. On the other hand progression to the chronic stage of hemorrhagic nephritis resembles in many ways a persistent infection in which the kidneys suffer continuous damage in somewhat the same manner as the heart suffers continuous damage during repeated exacerbations of rheumatic fever. Little by little the functional derangement of the kidneys begins to dominate the clinical picture just as the failing circulation dominates the clinical picture in rheumatic heart disease. The complicated and dramatic symptoms of renal failure gradually demand the undivided attention of the physician and in an effort to understand combat and relieve these he is likely to overlook the fact that the disease is still in the acute stage.

It is desirable to consider the patients who have been under investigation in more detail. To do this they will be discussed in four groups. Group I is comprised of those patients who have recovered. Group II of those who are in the latent stage. Group III is comprised of those in the active stage and Group IV of those who have died.

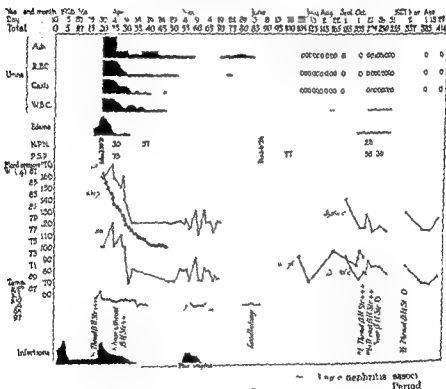
**Group I—26 Cases.**—In 9 of the 26 cases the primary attack was severe enough to require hospitalization.

was evident. Within a few days or at most weeks the pronounced



symptoms subsided, the infection improved and the majority of these patients began to convalesce. In most of these patients, however, even though the infection was eliminated, the urine continued to show small amounts of albumin, casts of various kinds and red blood cells for weeks or, indeed, months before normal conditions were reestablished. Case 1 (Fig 68) illustrates the course of the disease in 1 of these 9 patients who, after a severe initial attack, recovered quite promptly. Case 3 (Fig 70) is an

Acute Nephritis with Toxic Illness and Septicemia  
by T. P. and Dr. J. D.



showed no physical signs of infection. A few casts and numerous red blood cells were found in the urine. The patient recovered quite promptly. The infection was eliminated, but the urine continued to show small amounts of albumin, casts of various kinds and red blood cells for weeks or, indeed, months before normal conditions were reestablished. The patient recovered quite promptly. The infection was eliminated, but the urine continued to show small amounts of albumin, casts of various kinds and red blood cells for weeks or, indeed, months before normal conditions were reestablished.



than three months in 3 patients, from three to six months in 4 patients, from six months to one year in 4 patients and for sixteen months in 1 patient. It may be seen, therefore, that mildness of onset does not always insure rapid recovery from acute hemorrhagic nephritis, for complete recovery did not take place in 5 of these 12 patients until six months had elapsed from the onset of

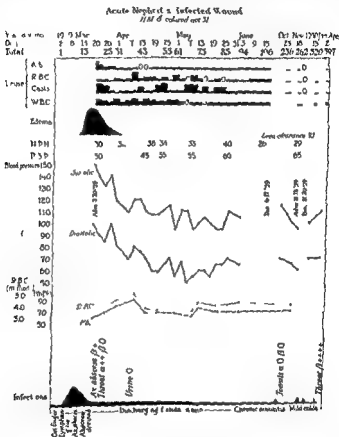


FIG 70—Case 3 H M Acute nephritis recovery from acute symptoms. Excellent physical health with normal tests of renal function but persistence of albuminuria, hematuria and cylindruria with presence of  $\beta$  hemolytic streptococci in tonsils. Eventual recovery.

the disease. Case 2 (Fig 69) illustrates, however, the course of the disease in a patient who developed a mild attack of acute hemorrhagic nephritis under observation, and in whom complete recovery took place within three and a half months from the onset. The patient was entirely well at the end of one and a half years, but has since been lost sight of.

In 5 of the 26 patients the onset was insidious and was only detected by examination of the urine. Careful examination in 1

and in 1 with scarlet fever. In 2 the initial stage lasted for less than one month, in 2 from one to three months and in 1 for three and a half months. Although the patients were asymptotically well in some cases even before the initial stage had subsided, abnormalities persisted in the urine for from one to three months in 3 cases and for one to two years in 2 cases. Reference has already been made to the importance of recognizing this mild form of the disease for the process may advance silently to the long latent stage and finally terminate with the characteristic signs of chronic glomerular nephritis. It is well known that some patients who are first seen in the terminal phase of the disease do not give a history of a previous attack of acute nephritis and it is quite possible that in some of these the disease began in the same insidious manner as that illustrated by the course of the disease in the last 2 patients. In both of them the acute process was associated with mild attacks of acute tonsillitis due to hemolytic streptococci of  $\beta$  type and in both there were sudden increases of albumin and red blood cells in the urine during the exacerbations of the tonsillitis. Both patients have been entirely normal to examination for more than five years.

When one compares the course of the infection with the course of the nephritis in this group of 26 patients who have recovered it is found that rapid disappearance or elimination of the infection was usually associated with more or less prompt recovery from the nephritis. It was not uncommon however to observe exacerbations of the symptoms and signs of the nephritis following tonsillectomy or with recurrence of the infection. These recrudescences of the nephritic symptoms were unlike the primary attack in certain respects. In the first place they were usually of mild character. Occasionally there was some return of the edema with an elevation of the blood pressure but more often the recrudescence was characterized only by a noticeable increase in the albuminuria, the cylindruria and the hematuria. In the second place, as had been pointed out above, the recrudescences differed from the primary attack in the time interval that elapsed between the operation or the acute infection and the onset of the nephritic recrudescence. It is well known that the primary attack follows the acute infection after an interval of one or two weeks with an average of about ten to twelve days while in some instances the first symptoms of nephritis do not appear until the patient is convalescent from the infection. The relapses and recrudescences

in these patients, on the other hand, came almost immediately after the operation or with the earliest symptoms of the infection. Gross hematuria has been observed from a few hours to twenty-four hours after tonsillectomy in patients who, previous to operation had had only microscopic blood in the urine. Elevation of blood-pressure, slight edema and an increase of the abnormal urinary constituents have been detected within the first twenty four or forty-eight hours of an acute infection. The difference, therefore, between the primary attack and the recrudescences in their time relation to the onset of the acute infection, or to the operative procedure, is a matter that is worthy of note.

Repeated observations and cultures from 24 of these 26 patients, over a period lasting approximately one to nine years, have shown that 20 have remained free from infections due to hemolytic streptococci, and have shown negative cultures since their recovery. Several of these patients have had other forms of infections. Many have had common colds, 1 has contracted syphilis. 1 or 2 have suffered from transient cystitis caused by *B. coli* and 1 has had a severe infection due to *Staphylococcus aureus*, about an unerupted wisdom tooth. Four patients have either shown a few  $\beta$  hemolytic streptococci in cultures from the pharynx on one or two occasions or have had definite infections due to this organism. In 2 of these 4 cases, single cultures from the pharynx showed  $\beta$  hemolytic streptococci many months after recovery. A third patient (Case 1) two years after recovery, had a severe attack of bronchitis caused by  $\beta$  hemolytic streptococci. She passed through the attack without the slightest evidence of a recrudescence of the nephritis and has continued well for four years. The fourth patient, a child who had an insidious form during an scarlet fever, has had enlarged tonsils and a severe infection by  $\beta$  hemolytic streptococci.

have been cultured on many occasions over a period of four years. In spite of the chronically infected tonsils there is no evidence of disease of the kidneys. Reference has already been made to the fact that patients, once they have recovered may pass through a severe infection by  $\beta$  hemolytic streptococci without experiencing exacerbations of nephritis.

**Group II—Latent, 14 Cases**—In this group the initial stages of the disease were in general similar to the types described for the acute form. The onset was severe.

stage was protracted, for in 8 patients it lasted for at least one to three months and in 5 patients for three to six months.

Twelve of these 14 patients are symptomatically well, and many

are at work. All are free from edema or show only traces of dependent edema on some occasions. In all of them the blood pressure is normal. All show some albuminuria; all but 1 have hematuria and many of the patients have a few casts in the urine. The Addis counts in 3 are only moderately abnormal. The disease which has existed in 3 patients for from three to eight years must be considered as slowly progressive unless one accepts the view that the nephritis may actually heal and yet the kidney bear a defect which allows the passage of abnormal amounts of albumin and formed elements. Volhard is inclined to believe that in some patients a persistent albuminuria and perhaps hematuria may be regarded as due to a 'Heildefekt' but the study which Addis has made of this important group of latent or quiescent cases makes it seem more probable that many or indeed most of them are progressive and end eventually, sometimes only after many years in the terminal stage. In 7 of the 14 cases the disease has lasted for from one to three years. Some of these patients seem to be improving steadily and it is still possible that complete recovery may ensue. In 3 patients the disease has lasted from nine to ten months and in these it is not possible to predict the eventual outcome. In 2 of the 3 it seems highly probable that complete recovery will take place. One patient was lost sight of after four months' observation.

In this group the course of the infection and the results of bacteriological examinations have been irregular. The patient who has shown recurring signs of nephritis for eight years has had repeated infections; the last an acute tonsillitis due to hemolytic streptococci of  $\beta$  type. Following tonsillectomy cultures from the pharynx continued to show  $\beta$  hemolytic streptococci. One patient

latent stage has persisted for five years showed hemolytic streptococci of  $\beta$  type on one occasion two years after the initial attack. Of the 7 patients who have had signs of nephritis for one to three years 1 has frequently given positive cultures of hemolytic streptococci of  $\beta$  type from the tonsils which have not been removed and 1 shows a persistence of this organism in the pharynx for long periods during convalescence. In 2 of the 7 patients hemolytic streptococci have never been isolated even from the primary infection and in the remaining 3 patients cultures made since the acute attack have been persistently negative. In the 3 patients in whom the disease has lasted less than one year, cultures have been repeatedly negative since the subsidence of the acute attack.

The ultimate outcome in this group cannot of course be predicted at present. It is a shifting group from which patients are trans-



albumin in the urine and the persistence of red blood cells and casts together with some elevation of blood pressure combined with intermittent dependent edema leaves little doubt that the disease is slowly but actively progressive. Eight cases belong to this type of which Case 4 (Figs 71 and 72) is a good illustration. All of these patients are living and in all of them the disease has lasted for two to seven and a half years. The renal functional tests show some impairment in all of the patients in whom it has been possible to make these tests but in Case 4 who has been

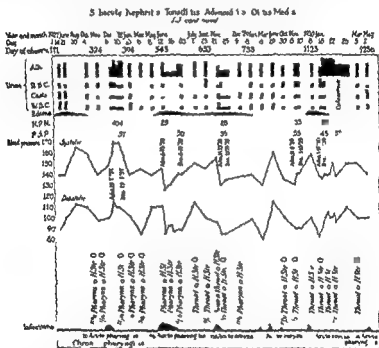


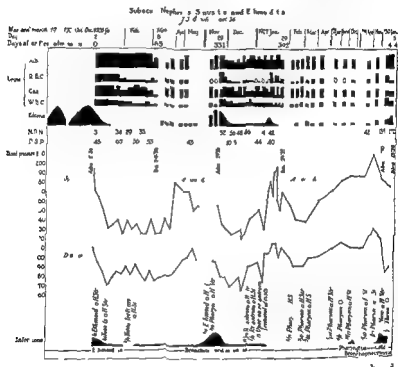
FIG. 72 (cont.) 1 to 5 (Continued)

under observation for six years the changes are comparatively slight. In another patient on the other hand who has been under observation for only two years the phthalein excretion and the urea clearance are both much reduced.

In the second type, the disease pursued a rapid and rather familiar course. In 7 patients the initial stage changed imperceptibly to the active stage which in 4 patients was characterized by massive and uncontrollable edema, moderate hypertension and marked albuminuria and hematuria. In the other 3 patients the edema



formed a less conspicuous feature, while the hypertension was marked. In at least 3, and perhaps 4, of the 7 cases, therefore, the nephrotic symptoms predominated the clinical picture and yet there seemed to be no question that there existed a hemorrhagic or diffuse glomerular nephritis, for hematuria was frequently profuse, the blood-pressure was elevated and the renal function greatly impaired. Two of these 4 cases came to autopsy. In both there were extensive degenerative changes in the tubular epithelium.



and in both of them there were diffuse, though moderate, acute changes in the glomeruli. The disease ran a rapid course in all 4 since only 1 patient lived as long as eight months. Indeed in this entire group of 7 patients the course of the disease was short for 5 of the patients died within a year of onset.

In a third group the disease ran a longer and somewhat different course. Two patients had an attack of



changes in the fundus oculi. Throughout the terminal stage the patients felt comparatively well. As the disease progressed a yellowish pallor of the skin with anemia became noticeable. Both patients died rather suddenly in uremia. Autopsy in Case 6 showed extensive chronic diffuse glomerular nephritis with some thickening of the intima of the arterioles of the kidneys. There were no changes in the arterioles of the other organs. In the other

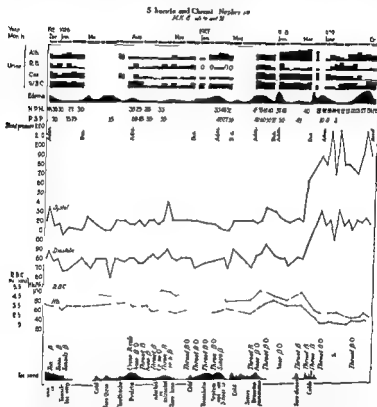


FIG. 75.—Case 7. M. K. Showing course of illness through nephrotic stage to hypertensive stage and death. Duration of disease four years.

2 cases (7 and 8) the initial attack was comparatively mild, and for long periods the disease ran the course of a moderately severe nephrosis without hypertension or measurable evidences of renal insufficiency. Shortly before death, however, hypertension developed rather quickly, the edema disappeared or became much less marked and the disease pursued the course already described for Cases 5 and 6. In Case 7 there were small colloidal exudates in the retina. In Case 8 there was an extensive hemorrhagic and

exudative retinitis. Both of these patients came to autopsy. In both patients the kidneys showed (Figs 76 to 78 and 79 to 82) extensive chronic diffuse glomerular nephritis, without changes in the arterioles.

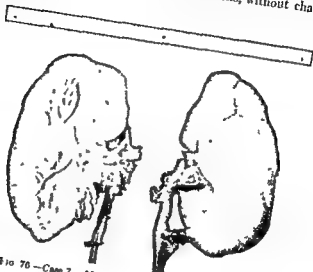
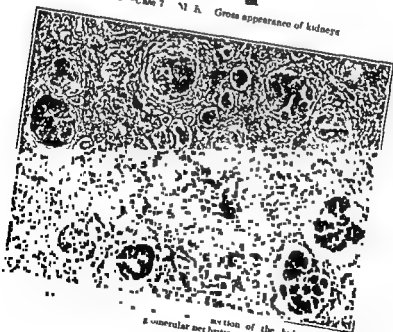


FIG 76—Case 7 N. R. Gross appearance of kidneys



Section of the kidney showing glomerular nephritis.

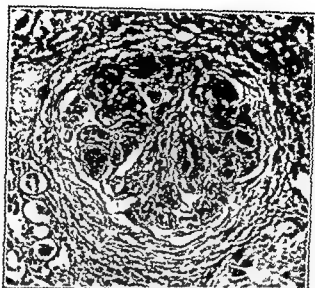
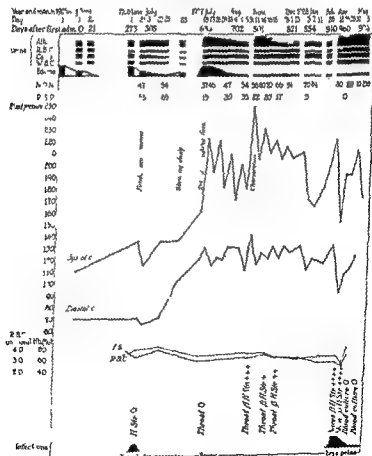


FIG 78.—Case 7 M K High power view of glomerulus

### Progress from Acute to Chronic Stage of Glomerular Nephritis



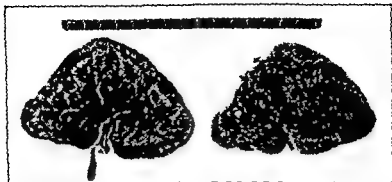


FIG 80—Case 8 T B Gross appearance of kidney (Bull Johns Hopkins Hosp)

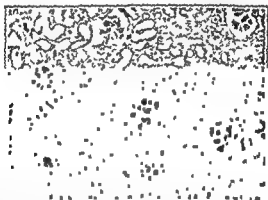


FIG 81—Case 8 T B Section of cortex showing extensive involvement of glomeruli with old crescent formation adhesions and moderate degree of infiltrations of interstitial tissues. (Bull Johns Hopkins Hosp)

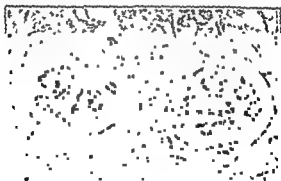
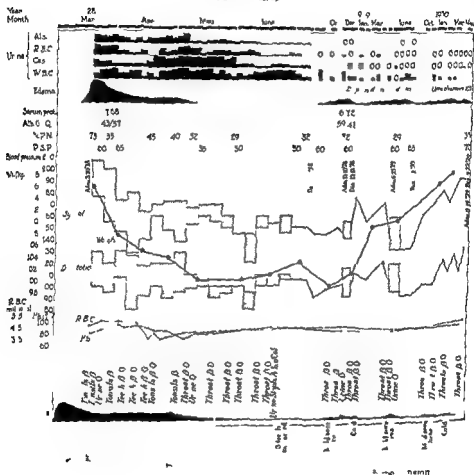


FIG 82 Case 8 T B Higher magnification of two glomeruli (Bull Johns Hopkins Hosp)

The fourth group is representative of a small number of patients who having passed through an attack of acute hemorrhagic nephritis have presented over a period of many years the clinical features typical of essential hypertension. Two patients have been

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ok served in whom the disease has run this course. One patient (Case 9) has been under observation for over four years, the second patient, also a woman, has been under observation for over six years and is symptomatically well. She is now working every day.

In both patients the initial attack of acute nephritis was rather severe but of comparatively short duration. Both patients have shown for a number of years considerable but irregular elevation of blood pressure and usually faint traces of albumin in the urine. Red blood cells have not been seen in the urine and hyaline casts are rarely observed. The renal function is good in Case 9 and was practically normal in the second cases when tests were made. One patient (Case 9) showed a transient perivascularitis of the retinal vessels during the acute attack of nephritis. The second patient

conclude that patients suffering from essential hypertension may, on rare occasions survive an attack of acute hemorrhagic nephritis and continue to live in comparatively good health for years afterward.

It is important to determine if possible what relation the infections that were observed in this entire group of 32 patients at the onset and during the course of the disease bore to the progress and termination of the nephritis.

In the 3 patients who died during the acute stage there were severe

in 1  
road

an infection by *Streptococcus viridans* was continuous.

In the 11 cases that died shortly after they were first seen and during the active stage of the disease 5 showed severe infections either during life or at autopsy. In 2 of them the infection was proven to be due to hemolytic streptococci of  $\beta$  type. Five of the 5 patients of the first type have had recrudescences of infection

able infections of the nasal sinuses due to hemolytic streptococci throughout the course of their entire illness while 1 patient had recurrent infections due to hemolytic streptococci. Both patients of the fourth type have been free as far as could be determined from infections caused by hemolytic streptococci for several years.\*

\* Case 9 has recently had erysipelas. During the acute illness there was no evidence of an exacerbation of nephritis.



# ETIOLOGICAL RELATION OF HEMOLYTIC STREPTOCOCCI TO ACUTE HEMORRHAGIC BRIGHT'S DISEASE

In reviewing all the data available at this time bearing on the relationship between the progress of hemorrhagic nephritis and the persistence or recurrence of infection one cannot escape the impression that there exists some connection between the two. Although it is possible that this relationship is merely a coincidence such a conclusion seems improbable. Reference has already been made to the difficulty of detecting and of completely eradicating the infections of the upper respiratory tract in these patients. At times chronic infections of the nasal sinuses have persisted or when they

is in reality a complication of the disease

TABLE 3? —THE COURSE OF NEPHRITIS IN RELATION TO PERSISTENCE OF INFECTION (ONE TO NINE YEARS)

Condition	No. of cases	Cultures or infections persist at or recurring	
		Positive	Negative
Well	24	4	20
Latent	14	6	8
Progressive active and fatal	32	24	8
	70	34	36

The close connection between infection by streptococci and the

considered to be in the  
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to be in the

The mortality in this series of young adults is high. This however conforms to the experience of others. Acute hemorrhagic nephritis in children is comparatively benign, but in the adult the disease is much more likely to progress to a latent or chronic state and terminate eventually in death.

Recovery from acute scarlatinal nephritis in children is so common that on surveying the statistics (Fishberg), it appears that unless death occurs during the acute phase of the disease, permanent recovery is the rule. Hansborg<sup>24</sup> examined 254 children, one to ten years after their acute attack of scarlatinal nephritis, and could find no abnormalities in 259. The prognosis seems less favorable, particularly in adults, when nephritis supervenes upon some other form of infection such as tonsillitis. Lichtwitz<sup>25</sup> records 64 cases of nephritis of which 8 became chronic, 3 died and 40 were discharged improved. An immediate recovery from the acute attack in less than 50 per cent. James<sup>27</sup> examined 67 children from three months to fifteen years after an acute attack of nephritis, the average interval being five years. He found that only 9, or 13.3 per cent, had terminated in a chronic form of the disease. Greenwood<sup>28</sup> obtained information concerning the subsequent course of 38 cases of acute and subacute nephritis two to seven years following therapeutic tonsillectomy. Most of the patients were under fifteen years of age. Twenty-three patients were reported in good health, while 10 had progressed to a chronic stage or had died. Clausen<sup>29</sup> reports 73 recoveries from acute or subacute nephritis in 129 children with 20 deaths and 9 cases progressing unfavorably. Aldrich<sup>30</sup> states that of 129 children suffering from acute postinfectious hemorrhagic nephritis 111 recovered, 8 died during the attack, 4 died of other causes, 5 were comatose and 1 was lost sight of. Little and Rosenberg<sup>31</sup> followed 30 cases of acute glomerular and acute diffuse nephritis in children for at least one year after the primary attack of these, 38 had recovered, 6 had died and the remainder progressed to a chronic state. Guild<sup>32</sup> has reviewed the entire subject of the prognosis of acute glomerular nephritis in childhood. Both from the study of her own cases and from those reported in literature she concludes that the outcome is generally favorable.

In the adult on the other hand complete recovery seems to be much less common than it is in children. The statistics for cases of Trench nephritis though incomplete in many respects show a surprisingly small number of recoveries. Though Toenniesen<sup>33</sup> states that out of 254 cases 68 per cent were discharged from the hospital as recovered statistics of Hume and Watson<sup>34</sup> "Deutsch" suggest<sup>35</sup> Magnus-Welken<sup>36</sup> and Gross<sup>37</sup> on the outcome of war nephritis in the British French and German armies show only from 17 to 49.5 per cent recoveries. Scheidel<sup>38</sup> examined 120 patients in 1910 and 1911 who had suffered during the World War with war nephritis. Of these, 18 per cent showed residual albuminuria,

varying in age from infants to seventy years as 55 per cent. They were able to examine 48 of 85 patients from eleven to twenty years after the acute attack. Two had died of chronic nephritis, 5 were alive but were suffering from chronic nephritis, 41 were well. This recovery rate differed from the acute stage in which there were

20 recovered, 21 of the remaining 45 patients over ten years of age recovered, which gives a recovery rate of 75 per cent. Omann<sup>45</sup> studied 56 patients who had had an acute attack of nephritis in childhood or early youth from eighteen months to twenty-two years after the attack. Of these 61.2 per cent were perfectly well while

does not occur in a very large proportion of cases.

In the authors' series death has occurred in 22 of 72 cases or in 30.5 per cent and complete recovery in 26 or only 36 per cent. Among the fatal cases are included however 2 instances of subacute bacterial endocarditis and 6 patients who were first seen during the late active stage of the disease. The criteria for complete recovery have in addition been rigid and it may be that several of the 14 patients now considered to be in the latent stage have in fact recovered from their disease. These statistics give therefore only an approximate idea of the severity of the disease and err in all probability on the side of pessimism. A few statistics are tabulated below and serve to contrast the mortality in children (Clausen) with that in the adult (Table 33).\*

It may well be questioned as to whether the attempts to eradicate infections in this group of 72 patients has resulted in any material benefit to them. In many instances it has been impossible to accomplish this with any degree of success but in a number of patients it has seemed that life has been prolonged by constant treatment of the infection or that recovery from the nephritis has occurred when the infection had completely healed and the infective organism had disappeared. There are undoubtedly

many other important factors that contribute to the ultimate out-

TABLE 34—PROGRESS OF ACUTE NEPHRITIS

Author	Total cases	Recovery		Latent		Progressive active	
		No.	Per cent	No.	Per cent	No.	Per cent
Hume and Varras	291	179	45.5	126	45.0	27	9.5
Deutsch	200	99	49.5	43	21.5	58	29.0
Siguet	47	8	17.0	92	46.7	17	36.3
Magnus-Alsleben	*		40.0		25.0		35.0
Cross	211	91	44.6	46	21.7	71	33.7
Longcope	72	26	36.0	14	19.4	32	44.3
Clausen	10	73	71.5			99	29.5

**Conclusions**—A description of the course of hemorrhagic nephritis is presented as it was observed in a series of 72 patients who were followed for periods of from one to nine years from the initial or early active stage of the disease.

In 26 or 36 per cent of these patients the disease ended with complete recovery; in 14 or 19.4 per cent of the cases the acute attack has been superseded by a more or less protracted latent stage; in 10 or 39 per cent the process is active and either slowly or rapidly progressive and in 22 or 30.5 per cent the disease has sooner or later terminated in death.

The relationship of infections, particularly of the upper respiratory tract to the onset and progress of the disease is discussed. Acute infections caused by hemolytic streptococci were found to precede directly or to accompany the acute attack of hemorrhagic Bright's disease in 72 of 76 patients or in 94.7 per cent. Evidence is presented to show that hemolytic streptococci are etiologically related to acute hemorrhagic Bright's disease. The disease, as it progresses from one stage to another may assume many different clinical forms. These variations depend upon several factors, but it appears from the clinical and bacteriological studies that are presented that an unfavorable progress is usually connected with exacerbations of the infection due to hemolytic streptococci or to persistence of this infecting organism, whereas recovery in the majority of instances is associated with disappearance of the infection or of the hemolytic streptococci.

Hemorrhagic nephritis may be regarded as an infectious disease. The onset is usually acute. During the progressive stages of the

30 per cent presented the picture of a chronic hypertensive nephritis and 47 per cent had progressive chronic nephritis with renal insufficiency. None were apparently perfectly well. McPhee and Hare give the mortality during the acute attack in a series of 90 patients varying in age from infants to seventy years as 5.5 per cent. They were able to examine 48 of 80 patients from eleven to twenty years after the acute attack. Two had died of chronic nephritis, 5 were alive but were suffering from chronic nephritis, 41 were well. This gives a recovery rate of 85.4 per cent. The recovery rate differed according to the age at which the patients suffered from the acute nephritis. All patients under ten years of age, of which there were 20, recovered. 21 of the remaining 28 patients over ten years of age recovered, which gives a recovery rate of 75 per cent. Osman<sup>42</sup> studied 56 patients who had had an acute attack of nephritis in childhood or early youth from eighteen months to twenty-two years after the attack. Of these 64.2 per cent were perfectly well while 35.7 per cent showed some signs of impaired kidney function, often with evidence of chronic nephritis. The studies of Addis too indicate that complete healing of the lesion in the kidneys in the adult does not occur in a very large proportion of cases.

In the authors' series death has occurred in 22 of 72 cases, or in 30.5 per cent, and complete recovery in 26, or only 36 per cent. Among the fatal cases are included, however, 2 instances of subacute bacterial endocarditis and 6 patients who were first seen during the late active stage of the disease. The criteria for complete recovery have in addition been rigid, and it may be that several of the 14 patients now considered to be in the latent stage have in fact recovered from their disease. These statistics give therefore only an approximate idea of the severity of the disease and err, in all probability, on the side of pessimism. A few statistics are tabulated below and serve to contrast the mortality in children (Clausen) with that in the adult (Table 33).\*

It may well be questioned as to whether the attempts to eradicate infections in this group of 72 patients has resulted in any material benefit to them. In many instances it has been impossible to accomplish this with any degree of success, but in a number of patients it has seemed that life has been prolonged by constant treatment of the infection, or that recovery from the nephritis has occurred when the infection had completely healed and the infective organism had disappeared. There are undoubtedly

\* "The 14 patients now in the latent stage of the disease are now being followed up. 100 cases, therefore, 40 per cent are in a progressive stage of the disease or have recovered from the disease."

many other important factors that contribute to the ultimate out-

TABLE III.—PROGRESS OF ACUTE NEPHRITIS

Author	Total cases	Recovery		Latent		Progressive active	
		No	Per cent	No	Per cent	No	Per cent
Hume and Natrass	981	178	45.5	126	45.0	77	9.5
Deutsch	900	99	49.5	43	21.5	58	29.0
Siguet	47	8	17.0	22	46.7	17	36.3
Magnus-Alesben	7		40.0		25.0		35.0
Gros	211	94	44.6	46	21.7	71	33.7
Longrope	72	26	36.0	14	19.4	32	44.3
Clausen	107	73	71.5			29	28.5

**Conclusions** A description of the course of hemorrhagic nephritis is presented as it was observed in a series of 72 patients who were followed for periods of from one to nine years from the initial or early active stage of the disease.

In 26 or 36 per cent of these patients the disease ended with complete recovery in 14 or 19.4 per cent of the cases the acute attack has been superseded by a more or less protracted latent stage in 10 or 3.9 per cent the process is active and either slowly or rapidly progressive and in 22 or 30.5 per cent the disease has sooner or later terminated in death.

The relationship of infections particularly of the upper respiratory tract to the onset and progress of the disease is discussed. Acute infections caused by hemolytic streptococci were found to precede directly or to accompany the acute attack of hemorrhagic Bright's disease in 72 of 76 patients or in 94.7 per cent. Evidence is pre-

sented. These variations depend upon several factors but it appears from the clinical and bacteriological studies that are presented that an unfavorable progress is usually connected with exacerbations of the infection due to hemolytic streptococci or to persistence of this infecting organism whereas recovery in the majority of instances is associated with disappearance of the infection or of the hemolytic streptococci.

Hemorrhagic nephritis may be regarded as an infectious disease. The onset is usually acute. During the progressive stages of the

infection, the kidneys are more and more seriously involved until in the advanced stages, the symptoms of renal failure dominate the clinical picture

CASE 1 — *Acute nephritis following infection of tonsils and sinuses by*  
*a* *low* *1* *t* *t* *g* *n* *m* *a* *g* *u* *l* *o* *n* *e* *s* *o* *f* *m* *a* *n* *h* *t* *a* *f* *o* *r* *e* *d* *i* *t* *y*

edema decreased and by April 10 examination showed T<sub>2</sub>  
e

January 1930 patient physically well Examination negative Blood  
and no albumin present  
clear  
t 400 cc  
0 blood  
t normal  
od cells

CASE 2

d scarlatina in childhood, occasional  
 ro and pleurisy two years ago On  
and  
ck

70  
 m  
 101

urine cloudy neutral no albumin few leukocytes } Cultures from throat  
show no  $\beta$  hemolytic streptococci

str  
on  
charged June 12 1929

TABLE 34 ADDIS COUNTS

Date	12 hr vol cc	Sp gr	pH	Prot mg. per 12 hr p	Red blood cells	Leuko cytes and epithelium	Casts
Apr 5 1929	243	1.017	5.0	101.9	136 000 000	22 500 000	1 015 000 (42% rbc cell)
June 6 1929	301	1.000	4.5	86.0	43 200 000	8 300 000	1 140 000 (16% rbc)
Nov 20 1929	460	1.000	5.5	66.0	2 06 000	3 000 000	27 000
Oct 1 1931	290	1.000		20.8	40 000	53 000	31 900 (hyaline 100%)



Case 4 4-1-1-1-1

course was charac-  
terized by edema  
and 72 The rec-  
treated by radium  
working regularly

white blood cells 7400 The condition remained practically the same  
during 1931 1932 and the first part of 1933 She worked daily On  
March 1  
over shi  
cent I  
cent nor  
globulin  
amount  
red bloo  
1 017

TABLE 35.—ADDS COUNTS

Date	1 <sup>st</sup> hr vol c	%p gr	pH	Prot mg per 12 hr p	Red blood cells	Leukocytes and epithelium	Casts
Nov 11 1931	490	1 013	6 6	1417	20 140 000	53 054 000	1 10 000
Mar 13 1933	605	1 017	uc	1650	2 400 000	10 600 000	300 500

CASE 5 *Acute nephritis progressing to chronic nephritis and death*

CASE 6—*Acute nephritis progressing to chronic nephritis and death associated with chronic infection of sphenoidal sinus by  $\alpha$  hemolytic streptococci* (Fig 74.) F S. Male white aged twenty years. Unit No 13197. Admitted August 14 1927 discharged November 16 1927

Chief complaint: Swollen head at — at

Go  
not  
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anc  
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hy a u b auu al auu u  
C it uue fu m thauu

CASE 8 — *Acute nephritis progressing through latent phase to chronic hyper*

r — — — — — 105°

Autopsy (No 10367) showed chronic glomerular nephritis

Weight 230 pounds Patient has been irregularly at work since October

no hemolytic she developed  
for six days  
olytic strepto-  
cocci was grown from left leg There was no generalized edema The  
urine during the acute erysipelas showed specific gravity 1.016 to 1.018

TABLE 36. ADDIS COUNTS

Date	Leukocytes	St. W.	pH	Prot. g. per 12 hr.	Red blood cells	Leukocytes and epithelium	Cells
Nov. 7 1931	19	100	6.6	III	240,000	16,540,000	23,000
Mar. 15 1933	180	101	ac	%	0	2,430,000	0

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## CHAPTER XXII

### A COMPARISON OF BLOOD-PRESSURE IN MEN AND WOMEN A STATISTICAL STUDY OF 5540 INDIVIDUALS

By MACNIDER WETHERBY, M D

**Introduction.**—This study concerns itself with the relative frequency of elevated blood-pressure among men and women. The basis for the study is formed by systematic observations upon 5540 individuals 2282 men and 3258 women. These individuals were all seen in the out-patient service of the University Hospital, University of Minnesota, during the three-year period from December, 1926, to December, 1929. The material has been subjected to the standardized mathematical analysis applicable to a material of this kind. In the course of the analysis certain results were obtained, lending themselves also to a brief additional discussion of normal blood-pressure.

As an introductory remark the statement seems justified that among the different phases of blood-pressure which have been the subject of study the pressure of young adults has been most thoroughly and satisfactorily investigated. The greatest interest no doubt has been given to the relation of blood-pressure to age, while the relation to sex has been relatively neglected. MacWilliam,<sup>17</sup> in his review, summarizes the general concept by stating that most observers report the pressure in women, at least in the first half of life, as 8 to 10 mm. lower than in men, Symonds<sup>18</sup> being an exception.

Wikner,<sup>19</sup> who found the same values for men and women between fifty and seventy years but above the age of seventy a 10 mm.

risks. Practically the only other available material consists of hospital populations, a material with a high negative selection, and of the part of the lower middle class and poorer class, which visits the latter not be compensated but both analyzed.

life insurance material and Wikner<sup>15</sup> the in-patients in the free hospital (St Erik) for chronic diseases in Stockholm. Exton, cited by Adams,<sup>1</sup> in a material of 5727 blood-pressure determinations from both rejected and accepted risks, found the incidence of elevated pressures (above 150 systolic and 100 diastolic) higher among women than among men in the ages above thirty years. Saller<sup>17</sup> analyzed a material of 2468 men and 1743 women from the out-patient service of the University Clinic in Kiel. From the age of twenty-one to thirty-five years, the systolic pressure was essentially the same for men and women, from the age of thirty-nine years on Saller found

age  
diastol  
higher  
the diastol  
age, the w  
the men  
strictly no

Saller from his material excluded all patients on whom the diagnosis was made of any disease known to be associated with either elevated or lowered blood-pressure. Gelman<sup>16</sup> analyzed a group of presumably healthy working people, 2641 men and 1120 women, practically all under fifty years of age. Below the age of thirty years there were more men than women with systolic pressures above 141 mm, between the ages of thirty and thirty-nine years 6 per cent of the men and 11 per cent of the women exhibited pressure above this figure, between forty and forty-nine years, the corresponding figures were 15 per cent of the men and 19 per cent of the women.

Gager<sup>9</sup> analyzed the systolic pressures in 1000 men and 1000 women consecutively examined in the Cornell Clinic. Under thirty

decidedly more women than men were found to carry pressures of 150 mm or more. From 40 to 49 years of age the difference was less



middle class This is checked by a special dispensary agency The patients come both from the city and from the rural districts and consist of laborers, farmers, housewives and working women Many have no medical complaint, but are examined as a routine procedure sometimes as a preliminary to tonsillectomy, sometimes for hospital employment A small percentage only come because of symptoms suggesting hypertension All patients admitted to the medical house service have been included in this study Excluded from the material were clear-cut cases of glomerulonephritis and aortic insufficiency It has been interesting to notice the infrequency with which the diagnosis of true nephritis has been made

**Technique**—The blood-pressure in all instances was determined with mercury manometers and by the auscultatory method The diastolic pressure has been considered as the beginning of the fourth phase that is, the point at which there is a change from a sharp to a gradual fall of pressure. It was observed soon after by the complete auscultatory method that the pressure was taken in the thirty minutes to one hour after the patient's blood pressure was taken after the history had been solicited and near the end of the physical examination In this way the factor of exertion was eliminated and the element of excitement reduced

§

¶

each of these groups has been compared as to sex and age distribution The age distribution has been analyzed by decades with the exception of the fifteen to nineteen years of age groups The age of the patient has been considered as that given, and not according to the nearest birthday although in many cases the patient will give his age at the next birthday when this is a month or two hence only

For the analysis standard statistical methods have been used \*

\* The following explanations and definitions might prove desirable

(a) The means are arithmetic averages based on 5 mm. groupings of blood pressure records

(b) The standard deviations of the distribution are the root mean square deviations

by the square

variation of the

distribution

of the squares  
taken

error is three

or more

(k) A measure of difference is given by Pearson's  $\chi^2$  test (Pearson Karl on the test of Goodness of Fit Biometrics 14 186 1923 1923)

(i) P gives the probability of a given  $\chi^2$  occurring in a normal variation of one sample

Figs 84 and 85 show for the men and for the women separately the frequency distribution of systolic blood pressure in percentage of their respective age groups. The charts have been constructed

ments the manometer scale is marked off in 2 mm intervals. Thus

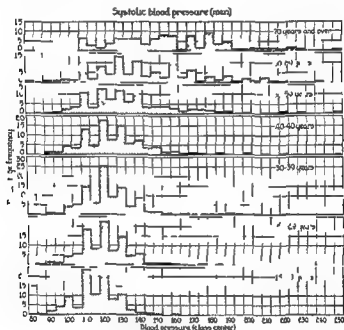


FIG 84 —Percentage frequency distribution of systolic blood pressure by 5-mm groups for men

there should be the same chances for readings on both sides of a 5 as around a 10. Actually this does not occur as shown by the charts. The charts further show a practically symmetrical distri-

seventh groups

Table 37 shows the mean values, standard deviations and coefficients of variability of the systolic pressure for the entire material,

## Systolic blood pressure (women)

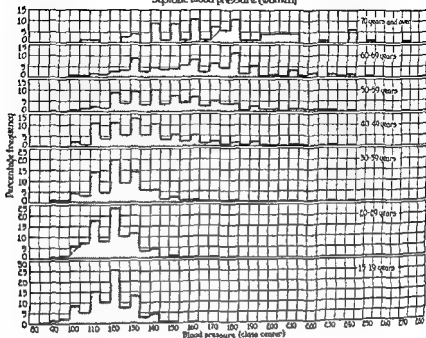


FIG 37 —Percentage frequency distribution of systolic blood pressure by 5-mm groups for women

TABLE 37 —SYSTOLIC BLOOD PRESSURE BY DECADES IN THE TOTAL MATERIAL

## Men

Age group years	No. of cases	Mean pressure (mm)	Probable error	Standard deviation (s)	Probable error	Coeff of variability
15-19	135	115.67	$\pm 0.74$	12.81	$\pm 0.32$	11.07
20-29	477	120.24	$\pm 0.42$	13.63	$\pm 0.30$	11.84
30-39	495	122.93	$\pm 0.40$	13.28	$\pm 0.28$	10.80
40-49	437	127.26	$\pm 0.68$	21.05	$\pm 0.48$	16.54
50-59	365	137.30	$\pm 1.02$	29.06	$\pm 0.72$	21.10
60-69	247	146.90	$\pm 1.25$	29.15	$\pm 0.88$	19.84
70 and over	126	158.10	$\pm 1.79$	29.66	$\pm 1.27$	18.69

## Women

15-19	285	117.93	$\pm 0.47$	11.81	$\pm 0.33$	10.01
20-29	731	119.55	$\pm 0.55$	12.94	$\pm 0.23$	10.82
30-39	786	125.83	$\pm 0.48$	19.79	$\pm 0.34$	15.73
40-49	636	139.43	$\pm 0.75$	27.92	$\pm 0.53$	20.02
50-59	513	152.92	$\pm 0.96$	32.04	$\pm 0.69$	20.95
60-69	241	163.92	$\pm 1.43$	32.97	$\pm 1.01$	20.11
70 and over	86	174.09	$\pm 2.83$	34.06	$\pm 2.00$	19.56

arranged according to sex and according to age, the latter expressed in decades (except for the age group fifteen to nineteen years) Both for men and for women there is a steady rise of the mean pressure from one age group to the other From the age of fifteen to thirty-nine years the rise is slight In the fifth decade (forty to forty-nine years) there is for the women a sudden rise of 14 mm, being just twice the rise in the preceding decade This rise brings the women 12 mm above the men, a difference which is not only maintained, but slightly increased during the following decades A sudden rise corresponding to the one just described occurs, to be  
 n in the women  
 the women has  
 pressure of the

This in a way is the main finding brought out in the present study, and the following discussion serves further to elucidate this point Attention shall be called to the fact that as this sudden break in the blood-pressure curve takes place, in the fifth decade for the women and in the sixth for the men, it is not only the mathematical mean that changes, but also the standard deviation and particularly the coefficient of variability, the latter becoming twice what

Table 37 and in Fig 86 that in the age group thirty to thirty nine years the mean pressure for the women is already slightly higher than the corresponding figure for the men, 2 88 mm to be exact

the commonly accepted requirement, that the ratio between the difference of the means and the probable error of the difference shall not be less than 3, it becomes evident from Table 38 (1) that the larger differences previously discussed possess a high degree of significance (the ratios for the age groups forty to forty-nine years and fifty to fifty nine years being 12 05 and 11 24, respectively), and (2) that even the small elevation of the mean pressure for the women between thirty and thirty-nine years above the corresponding mean for the men is of mathematical significance (the ratio being 4 64)

In order better to understand the meaning and significance of the changes in the mean pressures in men and women, a brief discussion seems useful before the presentation of any further tables It shall be remembered that the material under analysis consists of a practically unselected out-patient population, derived from

both city and rural districts—only instances of aortic insufficiency and definite chronic glomerulonephritis having been eliminated. One might conceive of three different phenomena as the possible cause of the gradual elevation of the mean pressures. There is first, the possibility that the pressure rises slightly in the population as a whole, further it might be that the elevations of the means are caused by a certain number of definite hypertensions mixed in

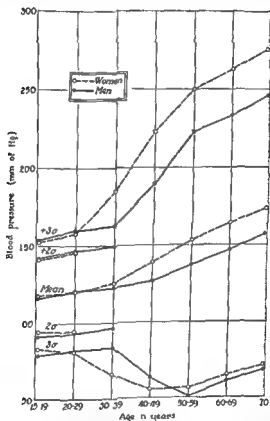


FIG. 86.—Means and standard deviations of systolic blood pressure of men and women in different ages

with a large group of normal people possessing pressures the same as in the groups below thirty years for the women or below forty years for the men. Finally, and this alternative presents itself, the increase in blood pressure with age may be due to a combination of two or more of these possibilities. Light is thrown upon these questions by Table 39

TABLE 2b —SEX DIFFERENCES BY DECADES FOR BLOOD-PRESSURE IN TOTAL AND ELEVATED SAMPLE

*Systolic Blood pressure*

Age group years	Total sample			Elevated sample		
	Diff (mm) women men	PE diff (mm)	Diff PE diff	Diff (mm) women men	PE diff (mm)	Diff PE diff
15-19	2.6	0.88	2.57			
20-29	-0.69	0.69	1.09			
30-39	2.88	0.62	4.84	1.43	3.04	0.47
40-49	12.17	1.01	12.06	5.84	2.40	2.43
50-59	15.62	1.39	11.24	0.46	2.21	0.21
60-69	17.02	1.80	9.00	5.44	2.40	2.26
70 and over	15.99	3.34	4.79	9.25	3.17	2.91

*Diastolic Blood-pressure*

Age group years	Total sample			Elevated sample		
	Diff (mm) women men	PE diff (mm)	Diff PE diff	Diff (mm) women men	PE diff (mm)	Diff PE diff
15-19	1.51	0.71	2.12			
20-29	-0.14	0.41	0.34			
30-39	0.26	0.44	0.59	3.71	2.55	0.87
40-49	4.01	0.55	6.91	2.90	2.03	1.42
50-59	4.40	0.74	5.94	0.45	1.50	0.30
60-69	4.99	1.06	4.71	0.72	1.65	0.44
70 and over	6.99	1.88	3.72	3.16	2.18	1.45

TABLE 30 —THE FREQUENCY OF SYSTOLIC BLOOD-PRESSURES ABOVE CERTAIN LEVELS IN THE DIFFERENT AGE GROUPS OF MEN AND WOMEN IN PERCENTAGE

*Men*

Min Hg	15-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70 years and over
150	1.48	2.94	4.84	12.38	26.31	42.88	61.90
160	0.74	1.26	2.61	7.12	18.63	34.38	46.82
180		0.21	1.40	2.99	8.50	15.36	29.56

*Women*

150	1.05	3.01	10.33	40.89	50.50	66.82	78.78
160	0.35	1.10	5.87	32.24	35.03	56.45	68.17
180		0.41	3.07	21.53	19.22	34.04	42.40

This table shows that a noticeable number of cases of moderate elevation of blood pressure start to appear ten years earlier among the women than among the men (thirty to thirty nine year group women vs forty to forty nine year group men). This incidence of rather moderate elevation of systolic pressure increases rapidly among the women but more slowly among the men as seen in the table where figures of the same order of magnitude for men and women have been underlined. Thus in regard to frequency of elevated systolic pressure the women in the age forty to forty nine year group are as badly off as the men twenty years later. This is well brought out for pressures above 150 and above 160 mm Hg.

A test of significance was made for the comparative incidence in men and women of the occurrence of a systolic pressure of 150 mm or over. Pearson's  $\chi^2$  test (see *h* in footnote page 372) gives a measure of difference which is interpreted directly on a probability scale. *P* (1 in same footnote) measures the chance that a difference would occur in a normal variation. Thus in Table 40 *P* = 0.8 corresponding to a  $\chi^2 = 0.1432$  in the fifteen to nineteen years of age group for systolic pressure means that there are 8 chances in 10 that the men and women in the given group are not differentiated with respect to the incidence of blood pressure over 150 mm or there are 2 chances in 10 that they are so differentiated. Table 40

TABLE 40 — COMPARATIVE INCIDENCE FOR MEN AND WOMEN OF SYSTOLIC BLOOD-PRESSURE OF 150 MM AND OVER AND DIASTOLIC BLOOD-PRESSURE OF 100 MM AND OVER

Age group years	Systolic blood pressure		Diastolic blood-pressure	
	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>
15-19	0.143	0.800	0.583	0.800
20-29	0.299	0.800	0.003	0.800
30-39	10.375	0.016	2.754	0.527
40-49	39.160	0.000	19.103	0.000
50-59	61.952	0.000	11.020	0.016
60-69	25.977	0.000	11.979	0.055
70 and over	6.139	0.106	3.740	0.295

Whether the elevated systolic pressures among women are of greater height than among men is tested in Table 41 which includes all individuals with a pressure of 150 mm Hg or more. If the means for the women are compared with the means for the men age group for age group and the differences tested as to significance in the usual way no significant difference between these two sets of figures is found to exist.

TABLE 41 — MEAN SYSTOLIC BLOOD-PRESSURES FOR THE GROUPS OF MEN AND WOMEN, WHOSE PRESSURE IS 150 MM Hg OR MORE

Men						
Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation ( $\sigma$ )	Probable error	Coeff of variability
30-39	22	169.36	$\pm 2.45$	17.05	$\pm 1.73$	10.07
40-49	52	169.36	$\pm 2.08$	22.20	$\pm 1.47$	13.11
50-59	91	177.43	$\pm 1.90$	26.87	$\pm 1.34$	15.14
60-69	103	174.89	$\pm 1.37$	20.60	$\pm 0.97$	11.78
70 and over	77	176.64	$\pm 1.63$	21.77	$\pm 1.15$	11.99

Women						
Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation ( $\sigma$ )	Probable error	Coeff of variability
30-39	73	170.79	$\pm 1.80$	22.76	$\pm 1.27$	13.11
40-49	177	175.21	$\pm 1.21$	23.84	$\pm 0.85$	13.60
50-59	247	177.89	$\pm 1.21$	26.23	$\pm 0.79$	14.74
60-69	156	180.33	$\pm 1.98$	36.63	$\pm 1.40$	20.31
70 and over	52	185.83	$\pm 2.72$	20.13	$\pm 1.93$	15.67

TABLE 42 — DIASTOLIC BLOOD PRESSURE BY DECADES IN THE TOTAL MATERIAL

Men						
Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation ( $\sigma$ )	Probable error	Coeff of variability
15-19	135	73.37	$\pm 0.59$	10.20	$\pm 0.42$	13.90
20-29	474	77.39	$\pm 0.33$	10.81	$\pm 0.24$	13.97
30-39	495	79.90	$\pm 0.34$	11.10	$\pm 0.24$	13.11
40-49	437	81.62	$\pm 0.44$	13.49	$\pm 0.31$	16.52
50-59	365	85.20	$\pm 0.56$	15.93	$\pm 0.40$	18.70
60-69	247	87.53	$\pm 0.74$	17.19	$\pm 0.52$	19.67
70 and over	126	87.86	$\pm 1.00$	16.67	$\pm 0.71$	18.97

Women						
Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation ( $\sigma$ )	Probable error	Coeff of variability
15-19	285	74.89	$\pm 0.39$	9.71	$\pm 0.27$	12.97
20-29	721	77.24	$\pm 0.25$	9.94	$\pm 0.18$	12.87
30-39	786	80.18	$\pm 0.23$	11.72	$\pm 0.20$	14.63
40-49	636	85.63	$\pm 0.35$	14.11	$\pm 0.27$	16.48
50-59	513	89.60	$\pm 0.43$	16.21	$\pm 0.34$	18.09
60-69	241	92.82	$\pm 0.76$	17.54	$\pm 0.54$	18.90
70 and over	66	94.85	$\pm 1.60$	19.23	$\pm 1.13$	20.27

the systolic There is, however, a steady rise in the mean pressure



by decades for both men and women. Until the fifth decade (forty to forty-nine years) the pressures are about the same in men and women. At this point the women show an abrupt rise their mean pressure exceeding that of the men by 4 mm. In the sixth decade the men show similar elevation of the mean diastolic pres-

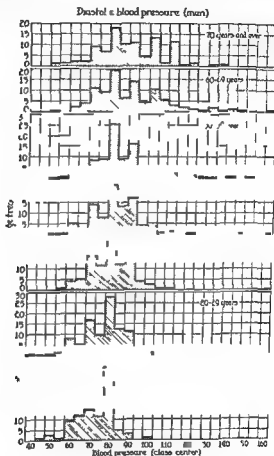


FIG 87 —Percentage frequency distribution of diastolic blood pressure by 5-mm groups for men

sure. There is a continued rise for the women so that the mean diastolic pressure for the women is higher than for the men in all decades of life over forty years. The standard deviations and the coefficients of variability rise much the same as for systolic pressure. The differences between the means for women and men are statistically significant in all age groups over forty years as shown in Table 38 though of lesser magnitude than for the systolic pressures.

Prior to forty years of age about the same percentage of men

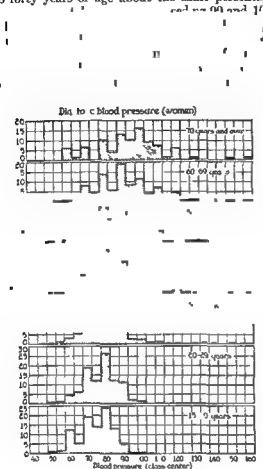


FIG. 8b.—Percentage frequency distribution of diastolic blood pressure by 5-mm groups for women

stolic pressures exceeding 100 mm Hg among men and women. For the age groups higher than forty years the  $P$  values indicate a definite probability that the women have a significantly higher percentage of diastolic pressures exceeding 100 mm Hg.

For individuals with diastolic pressures in excess of 100 mm Hg the mean pressures are about the same for corresponding age groups of men and women (Table 44). There are no significant differences (Table 38).

TABLE 43 — THE FREQUENCY OF DIASTOLIC BLOOD-PRESSURES ABOVE CERTAIN LEVELS IN THE DIFFERENT AGE GROUPS OF MEN AND WOMEN IN PERCENTAGE

Men							
Mm. Hg	15-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70 years and over
90	5.18	16.41	24.85	29.99	38.34	46.15	46.83
100	1.48	2.10	4.85	8.48	16.70	27.12	30.96

Women							
Mm. Hg	15-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70 years and over
90	7.36	15.60	24.03	40.26	50.70	62.66	69.73
100	1.05	1.92	6.09	16.83	24.17	34.45	45.48

TABLE 44 MEAN DIASTOLIC BLOOD-PRESSURES FOR THE GROUPS OF MEN AND WOMEN WHOSE PRESSURE IS 150 MM. HG OR MORE

Men						
Age group years	No. of cases	Mean pressure (mm.)	Probable error	Standard deviation ( $\sigma$ )	Probable error	Coeff. of variability
30-39	18	107.72	$\pm 0.19$	13.77	$\pm 1.55$	13.78
40-49	29	112.90	$\pm 1.90$	15.21	$\pm 1.35$	13.46
50-59	55	113.35	$\pm 1.26$	13.82	$\pm 0.89$	12.19
60-69	58	111.79	$\pm 1.19$	13.43	$\pm 0.84$	12.02
70 and over	36	108.11	$\pm 1.10$	9.76	$\pm 1.10$	9.02

Women						
Age group years	No. of cases	Mean pressure (mm.)	Probable error	Standard deviation ( $\sigma$ )	Probable error	Coeff. of variability
30-39	43	109.92	$\pm 1.30$	12.65	$\pm 0.92$	11.50
40-49	93	110.00	$\pm 0.71$	10.49	$\pm 0.51$	9.54
50-59	116	112.90	$\pm 0.81$	12.95	$\pm 0.57$	11.47
60-69	76	112.51	$\pm 1.15$	11.90	$\pm 0.82$	13.24
70 and over	28	111.36	$\pm 1.88$	14.76	$\pm 1.33$	13.26

**Discussion** The preceding analysis has revealed that women exhibit an elevated systolic blood pressure more frequently than men that this difference is noticeable already in the age group thirty to thirty nine years and becomes more marked in the following decade during which as many instances of elevated blood pressure are to be found among the women as one finds among the men who are twenty years older. Among the individuals who show a systolic pressure of 150 mm. Hg or thereabove men and women do not seem to differ in any significant way as to the degree of the elevation of the pressure.

We must remember that this is a statistical study of blood pressure and not a clinical study of hypertension consequently, no records of the presence of concomitant signs of hypertension (en

largement of the heart retinal arteriosclerosis etc) among the individuals exhibiting a pressure of 150 mm or more have been worked up for inclusion in this chapter. Neither has the constancy of the elevation of the blood pressure been studied in detail. Caution must therefore be taken in discussing to what extent the difference between men and women so clearly brought out by the

and others. If a greater blood pressure lability among women is the explanation for the differences brought out in this study then it becomes necessary to introduce a new assumption namely the development of such an increased lability among women above the age of twenty nine years since no trace of such a sex difference can be noticed in the two age groups below thirty years where not only the mean pressures but also the standard deviations are the same for both sexes. The author does indeed hesitate to introduce such a new concept.

There exist certain indications that chronic hypertension in its course and outcome behaves as a milder disease among women than among men. In the out patient service of the University Hospital where there is little difference between the number of men and women above the age of fifty years there are a number of women with elevated pressures but very few men who have been followed over a period of several years. Blackford Bowers and Baker<sup>6</sup> in a follow up study of patients with systolic pressures of 175 mm Hg or more found 65 per cent to be women while their general clientele did not show any such sex preponderance. Their patients were followed from five and a half to eleven years and showed during this time a mortality of 70 per cent for men and 39 per cent for the women. The average length of life after the diagnosis had been made was longer for the women than for the men. Riseman<sup>15</sup> likewise comments upon the relatively benign nature of hypertension in women.

Applying these facts to our problem a more benign course of

for the most surprising result of our analysis the early appearance of elevated pressures in the women between thirty and thirty nine years neither is it applicable for the great difference in the age between forty and forty nine years where out of the men there were only 12 per cent with pressure above 150 mm as versus 41 per

cent among the women. There exists no such mortality from hypertension or its sequels among men of this age to produce this sex difference among the surviving.

It is a matter of importance how to correlate with the findings of this study the results obtained from autopsies. We are fortunate to be able to compare with our blood pressure studies the detailed report by Bell and Clawson<sup>4</sup> based upon a large autopsy material from the same community as our patients. Bell and Clawson used hypertrophy of the heart (in the absence of valvular lesions or chronic glomerulonephritis) as the chief diagnostic sign (for details see original article<sup>5</sup>). Thus it is clear that only such elevated blood pressures as were sustained over sufficiently long time and at sufficiently high level to produce a marked hypertrophy of the heart can have become included in the study of Bell and Clawson. In their total material of 4578 autopsies on individuals between twenty one and eighty years of age, Bell and Clawson found 420 cases of chronic hypertension. Among these they found the corrected ratio of men to women as 1 1/4 to 1. For the whole hyper-

In the group of coronary sclerosis the ratio of men to women was 2.7 to 1. Eliminating the cases of coronary sclerosis the ratio for the remainder becomes 1.1 to 1. In the study of Bell and Clawson about 15 per cent of the individuals who died at an age above fifty years were afflicted with hypertension.

The author's statistical results are based upon the behavior of the systolic pressure to a greater extent than upon the diastolic though the diastolic reveals the same sex difference but less pronounced. Thus his material besides the elevation of systolic pressure also reveals a corresponding general increase in pulse

small autopsy material the hypertrophy of the heart was so pronounced. Thus the author believes indicates the line along which the discrepancy between his statistical results and results based upon autopsy material is to be interpreted.

On the basis of the previous discussion it seems justifiable to state that elevated blood pressures are found both earlier in life and with greater frequency among women than among men. From the type of the curves and character of the tables presented there seems to be no support for any correlation of the facts in regard to the women with the phenomenon of menopause. It further seems obvious that there exists a rather large number of individuals with pressures temporarily or permanently in excess of average levels.

It is with purpose that no word has been said about what constitutes a normal blood pressure—in order not to detract attention from the essential problem of this study. It might be of interest to return to Fig. 86 where on each side of the means lines have been drawn through points representing the distances from the means of three times the standard deviations ( $\pm 3\sigma$ ). According to established biometrical rules this distance three times the standard deviation represents the limit outside of which any given determination must fall in order to be considered as differing significantly from the mean. It should be added that in order to make such a rule hold it is essential that the material for which the mean has been calculated shows a practically symmetrical distribution such as the author's material does for the two lower age groups of Figs. 84 and 85. It should further be added that if this condition is fulfilled about 95 per cent or more of the single determinations from which the mean has been calculated will fall within plus and minus twice the standard deviation.

For the author's particular case only the material from the age of fifteen to thirty-nine years for the men and from fifteen to twenty-nine years for the women lends itself to a discussion of normal systolic blood pressure. On this point the reader is asked again to inspect Table 39 where the figures to the left of the — in the same line as 150 (mm Hg) well illustrate what has just been stated. Returning to Fig. 86 lines through the points representing plus and minus twice the standard deviation have been laid in for these age groups only ( $\pm 2\sigma$ ).

Practically all discussions of normal systolic blood pressure in man have been carried on with the hope of being able to draw a definite line of distinction between a normal pressure and an early pathological hypertension. Compared with the number of such attempts the discussions devoted to the differentiation between

once and for all between a normal pressure and an early hypertension is a futile one. As will be seen by comparing the figures in Table 39 for the age group twenty to twenty-nine years for instance with the blood pressure values represented by  $\pm 2\sigma$  and  $\pm 3\sigma$  in Fig. 86 the cases with blood pressures between the values of  $\pm 2$  and  $\pm 3$  times the standard deviation or between 147 and 160 mm Hg are insignificant in number and no one would dare to state on the basis of a single blood pressure reading whether they represent an early hypertension or not.

When cases of the same pressures start to accumulate in number as in the group of women between forty to forty-nine years for instance, they become significant in a different way now they form to a great extent the lower pressures among a group of hypertension as indicated in an indirect way by the enormous increase of the standard deviation of the mean for this group and we are statistically at a loss in determining the upper limit of a normal pressure for this age. We are at a loss because we possess no rule for a selection of our normal material, the needed dividing line being at the same time what we search for, and what we need to apply in order to find what we search.

For practical purposes the way out of this dilemma is the one followed by the actuaries of the life insurance companies: the determination of the pressure above which the death rate rises above the rate known to hold for the same age groups without elevation of blood pressure.

The author wishes to use this opportunity to express to Miss Marie M. Ness his appreciation of her invaluable aid in the statistical analysis.

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## CHAPTER XXIII

### ELEVATED BLOOD PRESSURE

By FRANZ VOLHARD M D

**Motto** In the high pressure I see the cardinal problem of the entire renal pathology

**Introduction** —The problem of hypertension is nearly a hundred years old. Today it occupies the center of interest, there are reasons to believe that its solution is not far away. The problem arose when Bright observed hypertrophy of the left ventricle of the heart among his cases of kidney disease. The knowledge of this puzzling relationship possibly is older, does not the Bible speak about "searching the heart and the reins"? When in the middle of the last century the tension of the pulse became the subject for intensive clinical studies, advances were necessarily made in regard to the occurrence, origin and significance of the hypertrophy of the heart in kidney diseases, from this hypertrophy an idiopathic heart hypertrophy was still held as a separate entity. When it finally became possible clinically to measure the pressure in the

The question was no longer *why* does the heart hypertrophy in many instances of kidney disease, but *how* does the hypertension arise both in kidney diseases and in the old 'idiopathic' hypertrophy and how explain a hypertension in patients not yet displaying any enlargement of the heart?

It is a commonplace statement that two factors are involved in the rise of blood-pressure, peripheral resistance and heart force or rather time volume. Thus the pressure will rise (1) as the result of an increase of volume flow, the peripheral resistance remaining constant and (2) by an increase in peripheral resistance, the volume flow remaining constant. Under the first alternative with a sustained increase of the output per beat we expect an "eccentric" length hypertrophy of the left ventricle, as in aortic insufficiency, in the second alternative with an increased peripheral resistance we expect a concentric hypertrophy chiefly in the thickness of the ventricular wall as in aortic stenosis. Since in pathological hypertension concentric hypertrophy is the rule, at least in well com-



penetrated early stages it might *a priori* be assumed that the rise in pressure is caused by increased peripheral resistance. In fact an increase in blood volume or in minute volume has not been demonstrated at least not with any degree of regularity. In regard to increased resistance the possibility exists that the viscosity of the blood is increased with the result that the flow through the finer vessels takes place with increased friction. This assumption should be abandoned. There are cases of hypertension with increased viscosity of the blood but more frequent are the cases of polycythemia and increased viscosity which present normal pressure.

The increase in resistance has been pictured as organic and attributed to alterations in the arterioles particularly in so called arteriosclerosis but also in acute nephritis. However in acute nephritis no changes can be demonstrated in the arterioles and in arteriosclerosis the characteristic lesions are present only in the kidneys

functional rather than organic.

The French are inclined to find the causative factor in a hyperadrenalinemia while in Germany one is accustomed to consider a central or reflex stimulation of the vasomotor center. This center regulates the blood pressure to a considerable extent through the bloodvessel bed controlled by the splanchnic nerves no great change of pressure takes place without the participation of the tonus and the filling of the vessels within the large region of the intestines. But splanchnic stimulation causes an increased outpouring of the hormone of the suprarenal glands and it seems questionable whether under physiological conditions one can produce an increase of blood pressure of any considerable duration without the participation of adrenaline. It has long been known

and on  
cluded that every rise of blood pressure brought about by the agency of the nervous system involves the cooperation of the chemical mechanism represented by the suprarenal glands. This conception has for many years been the subject of most vigorous attacks and deadlock seemed sometimes threatening. As usual the solution came through new and improved experimental methods which methods also gave results beyond the point under dispute. Generally speaking the problem was the clear-cut demonstration of the relative role of the chemical and the nervous factors in the control of circulation.

Improved methods for crossed circulation experiments seemed to promise results. Tournade, Chabrol and Marchand<sup>23</sup> made an

anastomosis between the suprarenal vein of one dog (B) and the jugular vein of another (A). Dog A had both suprarenals previously removed and dog B had the non anastomosed suprarenal removed. A nervous stimulation of the dog with the adrenal (B) thus will result in a chemical response in the dog (A) with both adrenals removed, while the dog with the adrenal (B) is capable of nervous response only.

Anrep<sup>2</sup> arranged for crossed circulation experiments by the use of one dog and a Starling's heart-lung preparation, in this way obtaining complete control over blood flow and blood pressure in the "donor," the heart-lung preparation, thus avoiding one source of error in earlier methods. This method still left the systemic circulation of the recipient dog uncontrolled. This disadvantage Anrep was able to overcome by a new technique which might be called an *innervated* heart-lung preparation which allows an independent control over the circulation in the brain and in the heart. Finally J. I. Heymans developed a method in which the circulation of the head of the recipient dog is taken care of by the donor, the recipient's head being completely separated from its own body except for the nerves within the sheaths of the two vagi. Though conflicts exist between the results obtained by different investigators, they are surprisingly few and it seems possible to obtain a view, at least grossly coherent of the mechanisms which regulate blood-pressure and circulation.

According to Tournade and Chabrol<sup>21</sup> on splanchnic stimulation of the donor (B) there occur in the same animal an immediate rise

stimulation of the donor (B) after a delay of ten to thirty seconds is followed by a marked rise in blood pressure lasting three or four

conditions and play a rôle in the maintenance of the vascular tone

When the blood pressure of the donor was reduced by bleeding adrenalin secretion resulted and the pressure in the recipient rose. The reverse occurred when the blood pressure in the donor was raised by intravenous blood injection by stimulation of the splanchnic on the suprarenalectomized side or by injection of adrenalin the adrenalin output from the donor diminished and the blood pressure fell in the recipient. Anrep and Daly<sup>2</sup> used the heart lung preparation to perfuse the lower half of a second animal (recipient). When the splanchnic of the recipient was stimulated or when anemia of the brain was produced in the recipient adrenalin was discharged as indicated by acceleration of the heart in the heart lung preparation and by the failure of this acceleration to occur if the suprarenals of the recipient had been previously removed or denervated.

Turning from the hormonal to the nervous regulatory mechanism the consideration of both central and reflex phenomena call for our attention. Such consideration by necessity deals with a multitude of combinations which though generally known are not easily kept clearly in mind. The informed reader therefore will have to overlook the repetition of facts which seem to him commonplace.

Of centers the vasomotor and the cardio inhibitory ones are of greatest importance. These names the reader will notice are functional only morphologically the former represents part of the sympathetic centers scattered in the medulla and might possibly be located near the nucleus of the facial nerve the latter is a part of the vagus center. Though Bayliss is correct in his statement that the substitution of the name vasomotor for the accurate vasoconstrictor may cause confusion the name vasomotor is commonly applied. These centers have been shown normally to respond to two different types of stimulation reflex stimulation from afferent impulses and central stimulation from variations in blood pressure within the centers themselves. Pathological response follows acute anemia asphyxia and altered composition of the blood. The receptors of the different reflex arcs normally respond to variations in pressure only. The efferent arcs from the vasomotor and cardio inhibitory centers are the sympathetic and the vagi respectively. Of afferent reflex arcs we know of two pairs the depressor nerves going in the vagi and the connections between the carotid sinus and the medulla said by Hering<sup>1</sup> to follow the glossopharyngeal and named the sinus nerves. Hering has named the depressors and sinus nerves *Blut druck uger*. The receptors of the depressors are spread over a wide area. Using the slowing of the heart as response and increased pressure as stimulation Daly and Verney<sup>2,3</sup> found receptors present in the ventricular wall of the heart and in the aorta as far onward as the upper part of the descending aorta. The receptors in the carotid sinuses are concentrated over a smaller area and seem to

have a maximum concentration right in the slightly sacculated carotid sinus.

Anrep and Starling<sup>2</sup> studied the effects of *central* stimulation of the vasomotor and cardio-inhibitory centers. Acting synergetically these centers control the blood-pressure in the following way. Inhibition of the vasomotor center causes vasodilatation, stimulation of the cardio-inhibitory center causes slowing of the pulse, the latter occurring when the vagi are intact and both reactions together lowering the pressure. A mechanical rise of the blood pressure in the brain inhibits the vasomotor and stimulates the cardio-inhibitory center. Or in terms of the actual experiments. When the blood-pressure in the brain was reduced, an immediate vasoconstriction in the animal took place, and *vice versa*, when the pressure in the brain increased an abrupt vasodilatation in the rest of the body occurred. Or again in general terms. *Changes in the blood-pressure in the vasomotor center produce the reverse changes in the blood-pressure in the rest of the body.* The effect is almost immediate, the latent period being measured in fractions of a second. The changes occur whether the vagi be cut or intact, they are based on a *central* mechanism and are vasomotor in origin. The rise or fall in the systemic blood-pressure produced by the reverse in the brain, is not of a transitory nature, but lasts until the pressure in the brain changes.

In regard to the heart-rate (Anrep and Starling<sup>2</sup>, Anrep and Segall,<sup>4</sup> Nash<sup>17</sup>), when the blood pressure in the brain was reduced an immediate acceleration of the heart followed, when the cerebral blood-pressure was raised the heart slowed down, these responses disappear after section of both vagi.

Asphyxia produced by cerebral anemia causes the blood pressure to rise and slows the pulse. Thus a stimulation is produced of both the vasomotor and cardio-inhibitory center at the same time, instead of the synergetic action of the two centers in response to a "physiological" stimulus we observe an antagonistic response following this "pathological" stimulation.

In regard to the *reflex* regulation of the blood-pressure, a rise of pressure in the aorta has exactly the same effect as a rise of pressure in the centers themselves producing an inhibition in the vasomotor and a stimulation in the cardio-inhibitory center resulting in a general vasodilation and fall in blood-pressure, together with a slowing of the pulse. These depressor effects are abolished on section of both vagi.

Hering's carotid sinus reflex represents a second reflex regulation of the blood-pressure identical as far as one can see, with the depressor mechanism just described in every respect, except the localization of its receptors in the region of the carotid sinus, the reflex usually is stronger on the right side than on the left (Hering,<sup>11</sup> Heymans<sup>12</sup>).

The main discrepancy which exists at present between the different investigators is that what Starling Anrep etc. have described as central regulation Hering and Heymans interpret as Hering's reflex regulation through pressure changes in the carotid sinus.

These facts then represent the high spots in our knowledge of the normal regulation of blood pressure. The author's sketch has been left incomplete. The reciprocal effect of the vagus and the sympathetic (the accelerator) on the heart rate he has not touched upon neither has he discussed the tone of the depressor and the sinus nerves the regulating effect of which becomes visible when it is abolished by section of these nerves a procedure followed by a sustained and under certain circumstances a most considerable rise in blood pressure. The possible existence of an independent pressor reflex and of independent vasodilators likewise purposely have been left untouched.

This sketch impresses upon us certain general principles in normal

for elevation of pressure. But the elevation might be overdone  
b. b. + he protected

predominantly as protective mechanisms against high pressure. The normal peripheral mechanism for the lowering of pressure is indeed an efficient mechanism. But still more is one impressed by the richly worked out reflex mechanism for setting this pressure reduction in action with pressure sensitive areas in the heart and aorta in the large arteries leading to the brain and in the brain itself. A further safeguarding of the undisturbed function of areas sensitive to extracerebral pressure is accomplished by the provision of separate nerve paths.

Still in spite of this seemingly fool proof mechanism deleterious chronic hypertension exists.

Against the background of the normal regulation of the blood pressure we proceed with the analysis of chronic hypertension. What is the relative importance of the two mechanisms the nervous

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 recognition of two distinct forms of chronic hypertension. Clinical observation led to such a recognition. Certain instances of high pressure must be caused by a contraction of all vessels in others this seems not to be the case.

In the first group the patients are pale in the second they are

ruddy. The kidneys of the first group at autopsy are found to be pale in the second red. The pale patients are sick, tired and weak.

constriction and the typical ischemic disease of the retina is apt

maximal narrowing of their arterial branches but not so in the red patients. In instances of pale hypertension one recognizes at a distance that the patient is ill with kidney disease; he presents the characteristic picture of a general arterial ischemia. The red ones rather figure as general hyperemias.

In the group of pale hypertension belong nephritic patients with tendency to develop retinitis angiospastica. The group termed red hypertension includes what once used to be called idiopathic hypertrophy of the heart and what today is usually named permanent or

disease picture though it may not have become more frequent yet has become better known. It is one of the great puzzles of present day medicine.

ical mechanism of pale hypertension are we dealing with an enrichment of the blood with the suprarenal hormone? After amounts of difficult methodical forework the author's co-worker Hulse, using arterial blood for his studies, was able to answer this question in the negative. Hulse's results speak against the doctrine of hyperadrenalinemia and also against the assumption of a central or peripheral excitation of the vasomotor center or of the splanchnic as the cause of the general vasoconstriction in pale hypertension—because such an excitation should produce a hyperadrenalinemia.

The assumption of a purely nervous origin of red hypertension likewise becomes improbable. Even if a short rise of pressure by purely nervous stimulation is possible through the effect of the splanchnic, we are dealing with a neuro-hormonal mechanism and the hormonal component could not remain inactive in sustained hypertension.

It is possible that instances occur in which paroxysmal or sustained hypertension is brought about by hyperadrenalinemia. Such might be the case in patients with hypertension and tumors in the suprarenals observed by others and by ourselves. It might also be the case in carbon monoxide poisoning and in transitory reflex

Normal Physiology

possesses no analogy to this pathological phenomenon. It falls not within the borders of the known. Each mechanism must be investigated and explained separately.

### THE CHEMICAL MECHANISM OF PALE HYPERTENSION

*Continuing his experiments* Hulse raised the question whether in hypertension substances are present in the circulation which sensitize the vessels to adrenalin. Animal experiments showed that the same amount of adrenalin always produced the same blood pressure effect, no sensitization resulting from repeated injections. Neither did the addition of normal human serum to the adrenalin have any effect upon the height or shape of the blood pressure curve resulting from the adrenalin injection. In contradistinction to these results, the addition of nephritic serum distinctly augmented the effect of the adrenalin. Serum from benign or red hypertension does not exercise the same sensitizing effect. For the latter group we had from clinical considerations already assumed no vasoconstriction to be present. This seemed to confirm our suspicion that an increase in peripheral resistance leading to hypertension might be produced in more than one way.

In hypertension with general vasoconstriction as exemplified in chronic diffuse nephritis the periphery seems the point of attack and the constriction appears to be chemically conditioned. An

patients with pale hypertension react to the smallest amounts of adrenalin intravenously injected with a rise of pressure whereas patients with red hypertension do not react to the same small doses.

Another step in the characterization of the serum of pale hypertension was taken through the observations of Kato and Watanabe<sup>6</sup> that the serum from chronic but not from acute nephritides has a sensitizing effect upon peripheral sympathetic fibers and more so the higher the blood pressure in the patient who supplied the serum. These workers tested the electrical excitability of the sympathetic observing the effect on the pupil. Tashiro<sup>5</sup> found this sensitizing

effect upon the sympathetic in sera from patients afflicted with chronic diffuse nephritis with hypertension and in malignant hypertension but not in essential or benign hypertension or in chronic glomerulonephritis without elevation of the blood pressure.

In animal experiments Major<sup>41</sup> has demonstrated a prolonged elevation of the blood pressure following injection of guanidine. In 15 instances of chronic nephritis Major concluded that guanidine was present in the blood in increased amounts (13 of these cases showed retention of nitrogen at the same time) and the same he found to be the case in 61 per cent of his hypertension patients. He did not differentiate between simple and malignant hypertension.

Concerning the chemical qualities of the sensitizing substance Hulse and Franke<sup>42</sup> have found it easily adsorbed by charcoal, soluble in alcohol, ether, acetone, and chloroform as well as water. After precipitation with alcohol the protein free plasma filtrate upon acid hydrolysis shows a definite increase in amino nitrogen with Van Slyke's method while such an increase is not obtained with

negative phenol reaction. Hulse and Franke<sup>42</sup> think of phosphatides and have especially suspected choline (amino-ethyl alcohol). Choline chloride after intravenous injection in curarized cats causes a long sustained marked rise of blood pressure.

Danzer, Brody and Mils<sup>43</sup> report on a pressor substance in whole blood from patients with hypertension. Their results were not confirmed by Curtis, Moncrieff and Wright<sup>44</sup> nor by Bodenstein.<sup>45</sup> Continuing on the author's suggestion the search for pressor substances, Bohm<sup>46</sup> found that an alcoholic extract of 30 cc blood from patients with pale hypertension produced in a cat a noticeable rise of pressure amounting to as much as 30 mm Hg and continuing for more than one half hour. Aqueous extracts from the blood of normal individuals and of patients with red hypertension caused the pressure to fall, so did the blood from 3 patients with focal nephritis and 3 patients with chronic nephritis without hypertension. At present blood has been examined from 70 normal individuals, nearly 100 patients with red hypertension and approximately 100 with pale hypertension. Results as described were obtained in nearly 90 per cent of the pale hypertensive material. This pressor effect occurred in animals even after section of the cervical cord indicating a peripheral action of the substance. The attack seems to be on the vessel wall, constriction having been observed of the surviving vessels of the rabbit's ear. Perfusion experiments on intestinal loops resulted in both arterial and venous constriction. Active extracts gave a stronger blue color with the ninhydrin reagent than inactive ones, pointing to a possibility of quantitative estimations.



The author feels that these observations of biological responses offer strong support for the assumption of a chemical mechanism of pale hypertension, an assumption independently arrived at through clinical observation and based upon the paleness, the narrowing of the capillaries and the angiospastic retinitis. As to the nature of the pressor substance or substances nothing can be said at present. Of immediate interest is the question of their origin and whether they are identical in all cases of pale hypertension. Possibly these substances originate from infections, particularly streptococcic infections including scarlet fever, or they might

It is clear that if it occurs in kidney damage only various kinds of damage will be drawn into our discussion

1 In a first group are included conditions in which the renal origin of the hypertension cannot be doubted (a) In every kind of anuria a rise in blood pressure is the rule (b) In urinary retention due to obstruction of the ureters by tumor, due to prostatic hypertrophy, narrowing of the urethra or to phimosis an elevated blood pressure is usually found. After removal of the obstruction the cases the heart will hypercondition which might be urinary obstruction or as a nephrons, hypertension is found as a rule (d) In pyelonephritic and hydronephrotic granular kidney hypertension is not infrequently present (e) The same is the case in hypoplastic kidneys

That occasionally hypertension is absent in any one of the groups just mentioned and in every group to be mentioned presently, does not invalidate the general rule, it does not even prove with certainty that an elevated pressure was not present during some part of the course of the disease

treatment and also after surgical reduction of the mass of normal kidney tissue. Correlating the clinical and experimental results of the biological test for pressor substances, positive findings have been obtained as follows in 2 instances of anuria, in 1 instance of

hypertension resulting from compression of the ureters by a car-

responsible for the appearance of the pressor substances in the blood. It might be recalled that Tigerstedt and Bergman<sup>12</sup> found pressor substances in extracts from normal kidneys.

■ In a second *angiopathic* group are brought together some conditions in which the high pressure seems to be renally conditioned (a) Rare instances of primary endarteritis of the renal arteries and (b) the very rare instances of hypertension in granular kidney due to amyloid.

Endarteritis of the renal arteries with secondary contraction occurs in syphilis and rarely in tuberculosis. Whether the hypertension in these cases develops prior to the renal insufficiency is not known. Here also belongs the endarteritis of the renal arteries which occurs as a part of the picture in periarteritis nodosa. In this peculiar infectious disease hypertension develops only when the kidneys are involved. Of this condition the writer has seen 1 patient resembling an acute nephritis with eclamptic uremia and a second one pre-ent-

ditions unfavorable for its development (Albrecht and von Brochowski<sup>10</sup>). The author has had occasion to observe cases of this kind due to syphilis. One patient died from renal insufficiency presenting the picture of eclamptic uremia retinitis angiospastica hyper-

\* He has succeeded of uremia. Autopsy showed the same severe amyloidosis as his brother had had.

The author feels that these observations of biological responses offer strong support for the assumption of a chemical mechanism

at present. Of immediate interest is the question of their origin and whether they are identical in all cases of pale hypertension. Possibly these substances originate from infections, particularly streptococcic infections, including scarlet fever, or they might enter the blood from the intestinal tract. Clinical and experimental facts point to the kidneys as the principal or only source.

An inquiry into the clinical conditions correlated with pale hypertension reveals that it occurs in kidney damage only. Various kinds of damage will be drawn into our discussion.

1. In a first group are included conditions in which the renal origin of the hypertension cannot be doubted. (a) In every kind of anuria a rise in blood pressure is the rule. (b) In urinary retention due to obstruction of the ureters by tumor, due to prostatic hypertrophy, narrowing of the urethra or to phimosis an elevated blood pressure is usually found. After removal of the obstruction the pressure might fall but in long standing cases the heart will hypertrophy. (c) In polycystic kidney, a condition which might be looked upon as the highest seated urinary obstruction or as a multiple hydrom, found as a rule

one of the groups just mentioned and in every group to be mentioned presently does not invalidate the general rule. It does not even prove with certainty that an elevated pressure was not present during some part of the course of the disease.

The following experimental findings may be correlated with the clinical conditions mentioned. In acute animal experiments hypertension will occur after destruction of renal tissue, after ligation of the renal artery on one side or after ligation of some of its branches and also after ligation of the ureter from one kidney (Hartwich). Hypertension is also the result in experiments on contracted kidney and in the kidney lesions

produced by transitory ligation of the ureters or by roentgen ray treatment and also after surgical reduction of the mass of normal kidney tissue. Correlating the clinical and experimental results of the biological test for pressor substances, positive findings have been obtained as follows: in 2 instances of anuria, in 1 instance of

hypertension resulting from compression of the ureters by a carcinoma of the uterus in 1 patient with polycystic kidney in animal experiments in hypertension produced by unilateral ligation of the renal artery and of the ureter

(b) the very rare instances of hypertension in granular kidney due to amyloid

Endarteritis of the renal arteries with secondary contraction occurs in syphilis and rarely in tuberculosis. Whether the hypertension in these cases develops prior to the renal insufficiency is not known. Here also belongs the endarteritis of the renal arteries which occurs as a part of the picture in periarteritis nodosa. In this peculiar infectious disease hypertension develops only when the kidneys are involved. Of this condition the writer has seen 1 patient resembling an acute nephritis with eclamptic uremia and a second one presenting the typical picture of genuine contracted kidney with a blood-pressure of 200 mm Hg and hypertrophy of the heart.

Almost as rare are the cases of uncomplicated amyloid contracted

due to syphilis. One patient died from renal insufficiency present

was confirmed histologically. A brother is alive\* with pronounced

\* He has since died of uremia. Autopsy showed the same severe amyloidosis as his brother had had.

The author feels that these observations of biological responses offer strong support for the assumption of a chemical mechanism of pale hypertension, an assumption independently arrived at through clinical observation and based upon the paleness the narrowing of

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1 In a first group are included conditions in which the renal origin of the hypertension cannot be doubted (a) In every kind of anuria a rise in blood pressure is the rule (b) In urinary retention

pressure might fall but in long standing cases the heart will hypertrophy (c) In polycystic kidney a condition which might be looked upon as the highest seated urinary obstruction or as multiple hydronephrosis of individual nephrons hypertension is found as a rule (d) In pyelonephritic and hydronephrotic granular kidney hypertension is not infrequently present (e) The same is the case in hypoplastic kidneys

That occasionally hypertension is absent in any one of the groups just mentioned and in every group to be mentioned presently does not invalidate the general rule it does not even prove with certainty that an elevated pressure was not present during some part of the course of the disease

The following experimental findings may be correlated with the clinical conditions mentioned. In acute animal experiments hypertension all occur after destruction of renal tissue, after ligation of

tension and hypertrophy of the heart in experiments leading to chronic kidney damage, as in the contracted kidney produced by chronic cantharidin poisoning or in the kidney lesions produced by transitory ligation of the ureters or by roentgen ray treatment and also after surgical reduction of the mass of normal kidney tissue. Correlating the clinical and experimental results of the biological test for pressor substances positive findings have been obtained as follows in 2 instances of anuria, in 1 instance of

that the kidney was the source of these pressor substances, the theory of eclampsia would have to be rewritten. Considering the frequency of compression of possible. Yet, so far, nobody

toxemias to be of renal origin permanent hypertension resulting in rare cases, in which instead of recovery typical endarteritic changes of the renal vessels develop? Here the pressor factor of pregnancy is not operating any longer. Must not here as in the chronic lead kidney the hypertension become renally conditioned? Do not these two types under these circumstances move back into the second or angiopathic group?

4 We have reached the pertinent problem of Bright's disease, the true hypertonic kidney diseases: diffuse glomerulonephritis or secondary contracted kidney and malignant sclerosis or genuine contracted kidney. In these diseases with tendency to retinitis angiospastica pale hypertension exists viz., a general vasoconstriction, chemically produced. In these forms of pale hypertension pressor substances are found in the blood. But serious disturbance of renal blood supply also exists. If disturbed renal circulation leads to the appearance of pressor substances in the blood, the conclusion evidently offers itself that a renally conditioned elevation

The most difficult problem is presented by the pathogenesis of acute diffuse glomerulonephritis, a condition characterized by a greatly disturbed circulation through the glomeruli, how does this serious circulatory disturbance originate? The author has assumed that in the acute stage this disturbed circulation is caused by vasoconstriction rather than by anatomical alterations. That besides the renal disturbance a general ischemia also exists is proved by the elevated blood-pressure and by the characteristic pale complexion of the patients, Hulse also demonstrated the presence of sensitizing and Bohn the presence of pressor substances in the blood. Is the glomerular vasoconstriction but a part of the general ischemia or is the peripheral vasoconstriction secondary to the renal process? The power of tradition supports the latter view while in favor of the former speak the observations of an elevated blood-pressure sometimes preceding the onset of renal symptoms. This interpretation would to a certain extent deprive the acute nephritis of its character of a primary kidney disease. It would be included in the third group of angiospastic kidney diseases together with the lead and pregnancy kidneys. Certain other observations speak against this

hypertension large liver and spleen and slight albuminuria. A sister and mother died under exactly the same conditions, whereas the father, who is responsible for this uncanny tragedy and who years ago had a cranial tumor disappearing after iodine enjoys the best of health.

Even in this angiopathic group the common factor operating in the elevation of the blood pressure might be sought in an inter-

sensitize the vessels to vasoconstricting and vasodilating substances (Wolpe<sup>40</sup>). Lead hypertension might be looked upon as due to

cases a typical contracted kidney results not to be distinguished from a severe secondarily contracted kidney. In such cases one might be more inclined to correlate the hypertension with the

Roenberg<sup>47</sup> Even taking into consideration the slow elimination of the lead after the poisoning has once taken place the question might be raised whether a disturbance of renal blood supply might not be the factor responsible for the sustained hypertension eventually leading to serious endarteritic lesions of the renal vessels.

may be looked upon as a part of a general vasoconstriction renally conditioned but responsible for the hypertension. As causative agents adrenalin like placental substances or biogenic amines have been suspected. Alder's<sup>48</sup> findings of elevated values for the amino nitrogen in eclampsia could not be confirmed by Hulse and Strauss<sup>49</sup> who suggest that Alder was deceived by the ninhydrin reaction. In the blood serum in eclampsia Hulse was able to demonstrate sensitizing substances. Bohn<sup>51</sup> found pressor substances and increased ninhydrin reaction. If it could be proved

Against the assumption of retention may be cited the fact that in pale hypertension a greater amount of them is found in the urine than in the case of normal individuals or of those with red hypertension. Again they might be products of disturbed metabolism.

such pressor substances appear in the blood. They are always present in retinitis albuminurica. The development of the retinitis and of renal insufficiency in hypertensive disease the author regards as effects of the pressor substances. The appearance of these substances in such a primary renal condition as polycystic kidney and after ligation of the artery or the ureter of one kidney supports the assumption that the kidney produces the conditions necessary for their appearance.

These substances, characteristic of pale hypertension, again are the cause of disturbed renal circulation with deterioration of kidney function—a vicious circle.

### RED HYPERTENSION.

So far, red hypertension has been characterized in a negative way only, and it is easier to state what it is not than what it is. It is neither caused by general vasoconstriction nor is it of chemical nor of purely nervous origin. It is not, as the author earlier used to believe, of renal origin. Possibly it is a

able to demonstrate typical lesions of the smaller arteries of the

investigators, particularly Wallgren,<sup>76</sup> confirmed the frequent association of these changes with essential or red hypertension. Red hypertension, however, occurs also without them. Impressed by the frequency of their coexistence, Jores<sup>67</sup> and also Wallgren suggested that the hypertension and the vessel changes were coordinated phenomena. Thus our problem becomes the demonstration of their common cause.

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viewpoint, namely the results of surgical interferences with the acute nephritic kidney, like decapsulation, splanchnic anesthesia and even diathermy or roentgen-ray treatment of the kidney region all intended to facilitate the circulation. Any one of these procedures in certain instances produces an almost instantaneous diuresis, lowering of the blood pressure and sudden recovery. Whatever the initial mechanism, the sustained vasoconstriction in the kidney must contribute to the maintenance and intensification of the general vasoconstriction.

Do we have to consider a twofold origin of the pressor substances, a primary extrarenal, correlated with the infection, and a secondary due to the disturbance of renal function or circulation—a "renin" production? Or is, as we used to believe, a nervously conditioned vasoconstriction within the kidney the primary factor and the general vasoconstriction the result of the disturbed renal circulation, as we experimentally found hypertension follow after ligation of the renal artery or the ureter? In acute nephritis as well as in these experimental conditions Bohn found pressor substances in the blood within only a few days after the blood pressure had started to rise. The appearance in acute nephritis of vasoactive substances with similar effect as in chronic renal hypertension the author looks upon as indicating that also in acute nephritis a disturbed renal circulation initiates the other symptoms. The difficulty shall be admitted in reconciling this view with the observations of what we may call "prenephritis," the appearance of an elevation of the blood-pressure prior to the onset of the urinary symptoms, as one might observe under the influence of a recurrent streptococcus infection, during recovery from scarlet fever, from acute tonsillitis or after "colds."

**Summary**—In any form of chronic hypertensive kidney disease leading to deterioration of kidney function the chemical mechanism of pale hypertension plays a rôle. A twofold relationship probably exists, the vasoconstricting substance or substances being the product of a diseased kidney and also a toxicant to the kidney, leading to renal insufficiency through lasting circulatory disturbances.

It seems likely that in certain acute conditions of pale hyperten-

will further be found in conditions of chronic disturbance of circulation, in certain but not all conditions of destruction of renal tissue and, as it appears, also when an insufficient amount of kidney mass is available.

Different possibilities evidently exist for the assumed relationship between the kidney and the appearance of pressor substances in the

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Against the assumption of retention may be cited the fact that in

and of renal insufficiency in hypertensive disease the author regards as effects of the pressor substances. The appearance of these substances in such a primary renal condition as polycystic kidney and after ligation of the artery or the ureter of one kidney supports the assumption that the kidney produces the conditions necessary for their appearance.

These substances characteristic of pale hypertension, again are the cause of disturbed renal circulation with deterioration of kidney function—a vicious circle.

## RED HYPERTENSION

So far red hypertension has been characterized in a negative way

able to demonstrate typical lesions of the smaller arteries of the kidneys in essential hypertension. Hypertrophy of the elastica of the prearterioles and hyalinization of the arterioles changes looked upon as belonging to arteriosclerosis were present. Subsequent investigators particularly Wallgren<sup>26</sup> confirmed the frequent association of these changes with essential or red hypertension. Red hypertension however occurs also without them. Impressed by the frequency of their coexistence Jores<sup>27</sup> and also Wallgren suggested that the hypertension and the vessel changes were coördinated phenomena. Thus our problem becomes the demonstration of their common cause.

In regard to the bloodvessel changes a twofold or even multiple increase in the thickness of the internal elastic layer in the prearterioles is recognized as a senile phenomenon. It might be looked

upon as the forerunner of arteriosclerosis and termed "presclerosis." Where degenerative changes, lipid deposits and hyalinization are present one must not be misled by the term.

#### Causative agents

What do we know about the cause of red hypertension? As in regard to arteriosclerosis in general, so also here all possible exogenous factors like alcohol, overeating, nicotine syphilis, psychic disturbances, etc., have been suspected as causes, but without sufficient proof. The only etiological factor about which there can be no doubt is age, *viz.*, the summit and decline of life. The fact that red hypertension is predominantly a disease of old age is usually not being sufficiently stressed. It very seldom occurs before the age of thirty, rarely before forty years, frequently between forty and fifty, and most commonly between fifty and seventy years. Women are affected nearly as often as men. Perhaps the red hypertension in women begins a little later than in men. In both sexes it is most frequently found between fifty and sixty years, between sixty and seventy years it is more common in women than in men. Table 45 and Figure 89 show the age and sex distribution of 719 patients with red hypertension in the writer's material.

TABLE 45 — AGE AND SEX DISTRIBUTION OF RED HYPERTENSION

Age	Men		Women		Total	
	No	Per cent	No	Per cent	No	Per cent
<20			2	0.7	2	0.8
21-30	6	1.5	1	0.3	7	1.0
31-40	27	6.3	15	5.1	42	5.8
41-50	57	20.6	62	20.9	119	20.7
51-60	160	37.9	92	30.9	252	35.0
61-70	109	25.8	58	30.0	167	27.4
71-80	32	7.6	34	11.4	66	9.2
51	1	0.2	3	1.0	4	0.5
	423 (58.7 per cent)		297 (41.3 per cent)		719 (100 per cent)	

erience heredity, emphasized by that one feels

inclined to credit the existence of a hypertensive constitution. Thus one is led to consider either a tendency to an abnormal vasomotor tone during the declining period of life or an inherited low resistance of the bloodvessel system. Those who emphasize the constitutional factor usually assume an abnormal excitability of the vascular system. The author leans more toward the assumption of an inferiority of the vascular system, manifested perhaps through an early vasoneurosis. It is, however, possible that the wear and

tear of a normal vascular system becomes accelerated through an inherited vasolability, expressing itself by abnormally strong and

the abnormal vascular excitability rather acquired and caused by the unknown mechanism of the red hypertension?

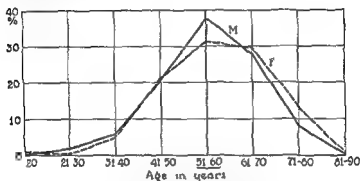


FIG. 1. — Age and sex distribution of 719 patients with red hypertension. Males 59 per cent females 41 per cent

The author does not consider gout or diabetes of causative impor-

diabetes are coordinated phenomena

At present old age and heredity remain the only important etiological factors and this must not be overlooked in the search for the mechanism of red hypertension. Pal<sup>n</sup> has offered the

most important factors of age and constitution. Let us rather inquire into the effect of old age upon the vascular system. Morphologically there takes place an augmentation of the elastica and of the connective tissue of the arterial wall functionally there is a diminution of extensibility. This has been proven for the aorta and the large arteries. Is it probable that the smaller arteries, in which the hypertrophy of the elastica is most apparent, remain free from this functional alteration?

The following considerations lead to the recognition of two clinical types of old age changes in the arterial system. (1) If the diminu-

tion in extensibility predominantly affects the aorta and the larger arteries, the "wind chamber" function of the vascular system will change in such a way that the normal volume output of the heart

show a greater lability than the diastolic (2) If the diminution in extensibility affects the smaller arteries chiefly, the systolic widening becomes diminished and the outflow resistance increased. A greater elevation of the diastolic pressure results and this elevation will show less lability. In both types, the blood-pressure will be greatly influenced by the minute volume of the heart. In the second type the blood, if its viscosity is increased, will meet with greater friction in the unyielding fine vessels and tend to raise the pressure. In neither type is it necessary to assume a changed tone of the arterioles nor a constant stimulation of the vasomotor center nor a central regulation of the pressure at an elevated level.

We are familiar with the first clinical type. As early as 1913 the author called attention to the fact that in the presence of a low diastolic pressure an increased pulse amplitude may constitute the only sign betraying arteriosclerosis of the aorta and large vessels, other condi-

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tensive material with the result reproduced in Table 46. Among "systolic hypertensions" Fineberg includes patients with systolic

TABLE 46—SYSTOLIC HYPERTENSION (FINEBERG)

Age	No. of hypertensive patients	Systolic hypertension	Per cent
Below 40	15	0	0
40-49	34	3	9
50-59	83	15	18
60-69	70	29	41
70-79	23	12	52
Over 80	12	7	58

strates a dominant increase of systolic pressure as a pronounced phenomenon of advanced age. Ten instances were necropsied, all showing marked generalized atheromatosis and vascular renal changes characteristic of hypertension. Heart hypertrophy was absent in one-half of the number of cases and when present, usually not pronounced. Fineberg considers systolic and diastolic hyper-

tension to be due to one factor, which causes a constriction of the peripheral vessels, and that a second factor must be added, which lowers the diastolic pressure this factor being atherosclerosis of the larger arteries. The author believes that the senile diminution of the elasticity of the large vessels and their atherosclerosis suffice to bring about this characteristic systolic hypertension.

The second clinical type with elevation of both systolic and diastolic pressures and marked decrease of dilatability of the small arteries may be identified as red hypertension.

There are individuals whose vessels are predestined to grow old early. One might picture the process which causes the diminution in elasticity as follows: During youth the blood pressure is carried exclusively by the smooth muscles which allow the vessels to dilate and contract within wide limits. The elastica safeguard against overdistention. With advancing age and a gradual and insensible stretching of the muscles the elastic elements of the vessel wall are called upon more and more often. A hypertrophy of the elastica and an increase in the connective tissue result. The more the elastica passively dilatability occurring in youthful vessels at very high pressures only is present in old vessels at slight pressure elevations. When this diminution in dilatability affects larger areas of the vascular system and particularly the smaller arteries diastolic pressure increase results from the difficulty in outflow. The wall of a severely dilated vessel might set up an increased vascular tone which will lead to muscular hypertrophy in vessels with powerful muscular coat and generally in vessels in which muscular insufficiency has not yet developed.

It is hardly necessary to add that the mechanism of the diastolic pressure in red hypertension is more complicated than this mechanical discussion indicates. May it suffice to point out that fever for instance will lower a high pressure. But attempts to live our ideas upon morphological facts cannot be dispensed with. Particularly in tissues which are mechanically used form and function are so closely associated that one cannot be comprehended without the other.

Hutchinson looks upon a certain degree of muscular and elastic hypertrophy of the arterial system as a constant result of every high pressure. Dietrich's studies of the changes in the larger arteries taking place with advancing age brought out important differences between the primary (the author's red) and the secondary nephritic (the author's pale) hypertension. With advancing age a decrease of the internal muscle fiber and an increase of elastic and collagen fibers occur whether hypertension is present or not. In the non-hypertensive the disappearance of muscular fibers is slight irregular

and disseminated. In red hypertension the disappearance of muscular elements is diffuse and more marked as is the increase in elastic and collagen fibers. There is also with great regularity a hypertrophy of the outer muscular coat and of the remaining fibers of the internal layer and finally a distinct dilatation of the vessel. In pale hypertension Dietrich found the same muscular hypertrophy but irregular and disseminated; the diminution of the internal muscular layer was lacking and the lumen only slightly widened. Lead hypertension showed similar changes. The findings were definite enough.

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The changes in red hypertension just described indicate an elevated tonus in response to the stretching caused by hypertension. The absence of dilatation and the more obvious hypertrophy of the better preserved internal muscular layer in nephritic hypertension may easily be correlated with the chemical mechanism of active vasoconstriction indicating that here we are dealing with hypertension caused by hypercontraction.

In red hypertension elastica defects are never missed in early changes of the media. Quite similar changes are also found in the arteries of the lower extremities in young people without hypertension. This might point to dilatation and fatigue of the tissue as a primary factor. We assume that the dilatation is accompanied by an increased mu-

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This again leads to increased stretching and instead of a purposeful compensatory mechanism we have actually a vicious circle.

It has already been mentioned that in essential hypertension marked elastic hypertrophy is to be found in special vascular areas particularly in the abdominal organs and most frequently in the kidneys. Johnson (1888) and Ewald (1877) early described hypertrophy of the media in the smallest arteries; yet lately relatively less attention has been given to this phenomenon. Fahr in 1927 called attention to the greatly reduced media in the renal vessels as compared with the well developed musculature of the small arteries of the skin, the intestines and particularly the skeletal muscles. Kernohan, Anderson and Keith "on biopsy material from the pectoral muscle of patients with hypertension have demonstrated a distinct muscular hypertrophy of the arterioles. Normally the ratio between wall thickness and lumen according to these authors averages 1 to 2 (1 to 1.7 to 1 to 2.7), in benign hyper

tension the ratio is distinctly higher, averaging 1 to 1.4 (1 to 1.1 to 1 to 1.8) and in malignant hypertension this change was still more pronounced.

Another important and nearly constant morphological finding in red hypertension is the so-called *arteriolosclerosis*. Different authors have offered different interpretations: (1) as the common form of the arteriosclerosis of the arterioles; (2) as the sought-for organic resistance which forces the pressure to rise; (3) as the result of the excessive load imposed by the high pressure.

The first interpretation the author does not consider correct. The second alternative likewise can be dismissed because arteriolosclerosis is never found diffusely in wide areas of the vascular system but nearly always in the abdominal organs only, with marked predilection for the kidneys.

However is not the fatty and hyaline degeneration of the arterioles which we name arteriolosclerosis at least responsible for the disturbed blood supply of the renal units bringing about their destruction and thus producing the granulated kidney of red hypertension? Most authors answer this question in the affirmative. But such an explanation is not well founded. As Hueck<sup>46</sup> has pointed out what closes the arterioles is a soft mass which would yield to pressure. We deal with *arteriolomalacia* rather than arteriolosclerosis and the changes must be the result of disturbed blood supply perhaps of a slowing of the circulation. If one accepts

pressure did not suffice to overcome the resistance so as to provide the terminal vascular structures with sufficient circulation. As shown by Hauch and especially by Baehr and Ritter<sup>47</sup> roentgen ray films of hypertension kidneys injected with barium reveal that not all large, middle-sized and small arteries have filled but the entire vascular tree is rarefied. On the other hand Ricker as well as Syvall<sup>48</sup> have shown that it is possible to inject hyaline arterioles which from their microscopic appearance were almost completely occluded. Arteriolomalacia to the author is a sign of disturbed blood supply present in red hypertension only when marked hypertrophy of the elastic layer is simultaneously present in the pre-arterioles. With it is associated a diminution of active and passive dilatability of the prearterioles and in this he sees the cause of the disturbed blood supply. It is the cause of the degeneration and obliteration of the arterioles and of the regressive changes of the glomeruli. That identical arteriolar changes occur in chronic nephritis is an additional fact in support of the conception that disturbance of blood supply is the cause not the result of arteriolosclerosis or



arteriolomalacia In nephritis there can be no doubt that serious  
circulation is affected.

for

the high pressure is easily derived from the above. The swollen wall of the arterioles indicates that the wall is no longer exposed to the high pressure existing within the larger ramifications of the arterial system. Arteriolomalacia follows upon high blood pressure but its cause is the diminution of circulation which results from the diminished dilatability due to elastic hypertrophy or abnormal muscular tone of the prearterioles. Senile or presenile changes of a constitutionally weakened vascular system.

In contrast to the active mechanism of vasoconstriction in pale hypertension we might speak of a *passive mechanism of red hypertension*. Passive insofar as we consider an overstretching of the arterial system the cause of the process. The isolated increase in systolic pressure the author likes to explain on the basis of the diminished elasticity of the large arteries. The increase in peripheral resistance which causes the elevation of the diastolic pressure may perhaps be explained in the following way. The overdilatation and hardening of the small arteries lead to a stretching of the

to this abnormal demand for distention the most minute arteries answer reflexly with increase of muscular tone and hypertrophy and thus bring about an increase in peripheral resistance. They are not in a stage of vasoconstriction but they have changed into a rigid system with a permanent tone preventing normal rhythmic relaxation.

This abnormal tone might well express itself also in the pathological excitability described as the hypertonic reaction type of the arterial system which most authors look upon as inherited.

sclerotic process we find the hypertonic diabetes of old age.

To summarize the discussion so far carried out the concept of a passive mechanism of red hypertension is based upon the assumption

stretching all processes commencing while a normal pressure still

exists and followed by an increased tonus of the arterioles via vaso-vascularis reflex

Another reflex mechanism may be thought of, a vasoneural reflex one over the so-called *Blutdruckzugler*, the depressor and sinus nerves. Contrary to what is frequently observed in the pale hypertension of nephritis red hypertension is not accompanied by a slowing of the pulse rate. One even observes patients usually with very high pressure and an unfavorable prognosis, in whom the rate stays above 90. What is then in red hypertension the rôle of the *Blutdruckzugler*? Evidently their receptor organs in the arterial wall are no longer responsive to the normal stimulus of intravascular pressure. Except for the receptors the reflex arc is capable of function as proved in some instances through the lowering of blood pressure following outside pressure upon the carotid sinus, as demonstrated by Hering.<sup>64</sup> It is inviting to correlate the lack of sensitivity of the receptors in the vessel walls with the decreased arterial dilatability discussed above. The condition as it exists might be considered as a decreased tone of the *Blutdruckzugler* and compared with the experimental results when this tone is abolished by the section of the depressor and sinus nerves, an operation resulting in sustained hypertension (Hering Heymans). What happens under these circumstances to the hormonal stimulation unavoidable as a part of splanchnic stimulation? Heymans has ascribed to the carotid sinus a regulatory influence upon the secretion of adrenalin. Goormaghtigh and Elaut,<sup>65</sup> of the same university as Heymans have studied the effects of this experimental hypertension upon the suprarenals. The section of the nerves results in

findings indicate a constant hyperfunction of the medulla and clearly demonstrate marked thickening of the cortex, caused by greatly increased cholesterol content.

One might well say that compared with other known internal secretions adrenalin possesses the most prompt and violent action, as demonstrated perhaps most strikingly through its effect upon metabolism (Boothby and others). The suprarenal veins thus function as the excretory ducts for a powerful and dangerous secre-

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zicher) From either viewpoint the mighty muscular hypertrophy

arteriolomalacia. In nephritis there can be no doubt that serious circulatory disturbance is present as a result of vasoconstriction.

The author's position in regard to the third interpretation offered for arteriosclerosis as the result of the excessive load imposed by the high pressure, is easily derived from the above. The swollen wall of the arterioles indicates that the wall is no longer exposed to the high pressure existing within the larger ramifications of the arterial system. Arteriolomalacia follows upon high blood-pressure but its cause is the *diminution of circulation*, which results from the diminished dilatability due to elastica hypertrophy or abnormal muscular tone of the prearterioles, senile or presenile changes of a constitutionally weakened vascular system.

In contrast to the active mechanism of vasoconstriction in pale hypertension, we might speak of a *passive mechanism of red hypertension*. Passive, insofar as we consider an overstretching of the arterial system the cause of the process. The isolated increase in systolic pressure the author likes to explain on the basis of the diminished elasticity of the large arteries. The increase in peripheral resistance which causes the elevation of the diastolic pressure may perhaps be explained in the following way. The overdistention and hardening of the small arteries lead to a stretching of the

answer reflexly with increase of muscular tone and hypertrophy, and thus bring about an increase in peripheral resistance. They are not in a stage of vasoconstriction but they have changed into a rigid system with a permanent tone preventing normal rhythmic relaxation.

This abnormal tone might well express itself also in the pathological excitability, described as the hypertonic reaction type of the arterial system, which most authors look upon as inherited, but which rather might be acquired. We might properly speak of an *angiosclerosis*, signifying something different from atherosclerosis, hardening only of the wall of the small arteries accompanied by elastica hypertrophy, which diminishes its active and passive dilatability. Where the pancreas is seriously affected by the angiosclerotic process, we find the hypertonic diabetes of old age.

To summarize the discussion so far carried out, the concept of a passive mechanism of red hypertension is based upon the assumption

stretching all processes commencing while a normal pressure con-

exists, and followed by an increased tonus of the arterioles via vaso-vascularis reflex

Another reflex mechanism may be thought of, a vasoneural reflex one over the so-called *Blutdruckzugler*, the depressor and sinus nerves. Contrary to what is frequently observed in the pale hypertension

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above 90. What is then in red hypertension the rôle of the *Blutdruckzugler*? Evidently their receptor organs in the arterial wall are no longer responsive to the normal stimulus of intravascular pressure. Except for the receptors the reflex arc is capable of function, as proved in some instances through the lowering of blood pressure following outside pressure upon the carotid sinus, as demonstrated by Hering.<sup>44</sup> It is inviting to correlate the lack of sensitivity of the receptors in the vessel walls with the decreased arterial dilatability discussed above. The condition as it exists might be considered as a decreased tone of the *Blutdruckzugler* and compared with the experimental results when this tone is abolished by the section of the depressor and sinus nerves, an operation resulting in sustained hypertension (Hering, Heymans). What happens under these circumstances to the hormonal stimulation unavoidable as a part of splanchnic stimulation? Heymans has ascribed to the carotid sinus a regulatory influence upon the secretion of adrenalin. Goormaghtigh and Elaut<sup>45</sup> of the same university as Heymans, have studied the effects of this experimental hypertension upon the suprarenals. The section of the nerves results in an immediate stimulation of suprarenal activity, visible within a few hours in greatly reduced chromaffinity. This acute exhaustion is overcome. After four months of hypertension the findings indicate a constant hyperfunction of the medulla and clearly demonstrate marked thickening of the cortex, caused by greatly increased cholesterol content.

One might well say that compared with other known internal secretions adrenalin possesses the most prompt and violent action, as demonstrated perhaps most strikingly through its effect upon metabolism (Boothby and others). The suprarenal veins thus

pretation having been given. Against the assumption that these

arteriolomalacia In nephritis there can be no doubt that serious circulatory disturbance is present as a result of vasoconstriction

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rigid system with a permanent tone preventing normal rhythmic relaxation

This abnormal tone might well express itself also in the pathological excitability, described as the hypertonic reaction type of the arterial system which most authors look upon as inherited but which rather might be acquired We might properly speak of an *angiosclerosis*, signifying something different from atherosclerosis, hardening

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of its different structural units, microscopically visible in cross-section of the internal muscular layer, defects in the elastic layer and overstretching all processes commencing while a normal pressure still

## RED HYPERTENSION

exists and followed by an increased tonus of the arterioles via vaso-vascularis reflex.

Another reflex mechanism may be thought of a vasoneural reflex one over the so-called *Blutdruck-nigler* the depressor and sinus nerves. Contrary to what is frequently observed in the pale hypertension of nephritis red hypertension is not accompanied by a slowing of the pulse-rate. One even observes patients usually with very high pressure and an unfavorable prognosis in whom the rate stays above 90. What is then in red hypertension the role of the *Blutdruck-nigler*? Evidently their receptor organs in the arterial wall are no longer responsive to the normal stimulus of intravascular pressure. Except for the receptors the reflex arc is capable of function as proved in some instances upon the lowering of blood pressure following outside pressure upon the carotid sinus as demonstrated by Hering. It is inviting to correlate the lack of sensitivity of the receptors in the vessel walls with the decreased arterial dilatibility discussed above. The condition as it exists might be considered as a decreased tone of the *Blutdruckzugler* and compared with the experimental results when this tone is abolished by the section of the depressor and sinus nerves. What happens under these circumstances to the hormonal stimulation unavoidable as a part of splanchnic stimulation? Heymans has ascribed to the carotid sinus a regulatory influence upon the secretion of adrenalin. Goormaghtigh and Flaut of the same university as Heymans have studied the effects of this experimental hypertension upon the suprarenals. The section of the nerves results in an immediate stimulation of suprarenal activity visible within a few hours in greatly reduced chromaffinity. This acute exhaustion is overcome. After four months of hypertension the findings indicate a constant thickening of the cortex caused by greatly increased cholesterol content.

One might well say that compared with other known internal secretions adrenalin possesses the most prompt and violent action as demonstrated perhaps most strikingly through its effect upon metabolism (Boothby and others). The suprarenal veins thus function as the excretory ducts for a powerful and dangerous secretion. Attention has long been focussed upon the peculiar muscular arrangements in the walls of these veins without a convincing interpretation having been given. Against the assumption that these seemingly irregularly arranged longitudinal muscle bundles serve the expression of adrenalin from the glands the opposite function is suggested that through contraction they affect the lumen of the veins and regulate or tend to regulate the rate of discharge (Goldzieher). From either viewpoint the mighty muscular hypertrophy

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of cause and effect in hypertension

The problem of the so-called *malignant hypertension* or malignant nephrangiosclerosis will finally be considered

As long as the passive mechanism of red hypertension prevails renal insufficiency does not occur. We are dealing with a benign disease insofar as the kidneys are concerned a benign nephrangio sclerosis and we distinguish a cardiac cerebral or pancreatic course of the condition. In the

course leads to renal insufficiency and true uremia the genuine contracted kidney. The sudden turn in the course of the disease has never been fully understood. The consideration of a typical instance brings out the differences from red hypertension. The patient is pale the capillaries extremely contracted the eyegrounds frequently reveal the first sign of the fatal turn in form of contracted arteries and the classical picture of retinitis angiospastica. Histologically the kidneys show the same characteristic ischemic reactions as in acute and subacute nephritis. Particular attention is called to the small arteries where inside the hypertrophic elastic layer one finds the endarteritis obliterans which is characteristic of the active mechanism of vasoconstriction. It consists of endothelial proliferation and an increase of subendothelial connective tissue in vascular occlusion changes not observed in red hypertension. The endarteritis and the occasionally coexisting arteriolonecrosis are definite histological signs of marked arterial constriction. Vasoactive pressor substances are found in the blood prior to any demonstrable impairment of renal function. The blood pressure is increased above the level of the red hypertension particularly the diastolic. The angiospastic closure of the vessels leads to the death of numerous glomeruli with destruction of secretory units all  
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In regard to the cause of this fatal turn at present the following only might be said. The cause cannot be found in impaired renal function since retinitis angiospastica as already stated frequently occurs earlier than any demonstrable decline of function. Bohn in a group of patients found pressor substances even before the occurrence of retinitis. The clinical course proved these instances as intermediary cases. Though the histological findings make the disturbance of renal blood supply a certainty the elastic hyper

trophy in the smaller arteries already discussed do not constitute the most important histological change. As such the author is inclined to recognize the muscular hypertrophy.

The age of the patient and the height of the diastolic pressure seem to be factors of special importance. The younger the individual in whom a genuine hypertension has developed and the higher his diastolic pressure, the greater is the danger of a malignant course. In contradistinction to the sex distribution of red hyper-

TABLE 47—AGE AND SEX DISTRIBUTION OF MALIGNANT HYPERTENSION

Age	Men		Women		Total		Per cent *
	No	Per cent	No	Per cent	No	Per cent	
20							0.3
21-30	2	1.6			2	1.3	1.0
31-40	17	13.8	4	11.8	21	13.3	5.8
41-50	45	36.6	14	41.3	59	37.6	20.7
51-60	47	38.2	10	29.3	57	36.3	35.0
61-70	9	7.3	5	14.7	14	9.0	27.4
71-80	3	2.5	1	2.9	4	2.6	9.2
	123 (83 per cent)		34 (21.7 per cent)		157 (100 per cent)		

\* Red hypertension (from Table 45)

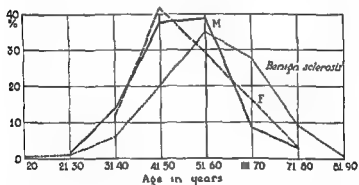


FIG. 90: Age and sex distribution of 157 cases of malignant hypertension. Males 78 per cent, females 22 per cent.

men and 22 per cent women as versus 39 and 41 per cent for red hypertension. The frequency among both men and women is high in the age groups forty-one to fifty and fifty-one to sixty, but drops off rapidly toward both sides. Between sixty-one and seventy years there seems to be relatively fewer men than women with malignant



hypertension Fig 90 for comparison also contains the age distribution for the total red hypertension material The curve for red hypertension is pushed forward just a decade later in life than the curves for malignant hypertension If we pool out whole material of genuine hypertension, benign and malignant we possess records of 876 patients, of which 157, or 18 per cent, presented a course characterized by retinitis angiospastica or renal insufficiency In the whole material there were 545 men and 331 women Of the men 22 per cent progressed toward renal insufficiency, of the women 10 per cent

An accurate understanding of the malignant sclerosis will be possible only when we understand better the occurrence of pressor substances in the blood We used to look upon this condition as a

hematogenous hypertensive mechanism to the passive mechanism of red hypertension

High blood pressure is frequently looked upon as a symptom like fever The high pressure from hyperadrenalinemia in certain suprarenal tumors may be considered a symptom of suprarenal hyperactivity red hypertension as a symptom of general or splanchnic angiosclerosis while in malignant sclerosis the pale hypertension is not a mere symptom, but the cause of the fatal disease, it is the cause of the contracted kidney

One frequently looks upon hypertension as a compensatory mechanism to increase the blood supply of the kidneys In pale hypertension according to the concept developed in this treatise, there can be no question of any compensatory benefit derived from the high pressure The general vasoconstriction includes all the danger which threatens the kidney could the production of pressor substance be checked the prognosis would be fundamentally altered

In regard to red hypertension the question is more difficult to answer If one accepts the assumption of a decreased arterial dilatability as the cause of the pressure elevation, the blood-pressure increase becomes significant as a compensatory mechanism Through it is secured a normal nutrition of the organs involved Is it not the cause of the favorable span of life and the practically normal capacity of these individuals? Would not the blood supply to the kidneys as well as to other organs suffer if the insufficiency of the peripheral pumping mechanism of the small arteries were not compensated for by a high pressure and increased work by the heart?

According to Thomas's and our own (Donecke and Rothschild's) investigations the vascular resistance of the kidney can be appre-



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## CHAPTER XXIV

### BILATERAL NECROSIS OF THE RENAL CORTEX \*

By WALTER DE M. SCRIVER M.D.

**Incidence** — Bilateral necrosis of the renal cortex, also described as symmetrical necrosis or bilateral infarction, was apparently first described in 1886 by Juhel-Rénoy. In a search of the literature the author has been able to find 38 other cases which fall into this group. Four of these recovered so that pathological specimens were not obtained, but the clinical picture is so definite that it appears that up to a certain level the same process was present in all.

**CASE HISTORIES** In recent years the author has seen in the clinics at the Royal Victoria Hospital 3 cases of this type, with death and autopsy confirmation in 2 and recovery in 1. All were admitted to the Maternity Service, where they were observed at the request of the attending obstetricians. The pathological studies which are reported here in brief were made by Professor Oertel, to whom the author is indebted for permission to use them.

and erythrocytes

\* The first three cases described here have been reported in detail with Horst Oertel in the *Journal of Pathology and Bacteriology* 33: 1071-1094, 1930 under the title "Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis)".

the hospital. She was delivered of a dead fetus and the placenta was followed by a large old blood clot. For three days the

TABLE 48—CASE 1

Day post partum	Urine volume cc	Blood urea mg per 100 cc	Blood creatinine mg per 100 cc	Blood pressure
1	60			
2	11	53	3.47	160/110
3	1			160/100
4	0	125	4.23	143/100
5	0	154	4.0	135/95
6	0			140/90
7	0			135/85
8	0	171	6.60	
9	0			

CASE 2

1	450			
2	1300			
3	550			
4	0	195	6.5	140/75
5	0			135/80
6	0	191	6.4	125/80
7	3	239		140/60
8	0			160/80
9	0			

TABLE 49

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admission spontaneous abortion took place. Immediately after delivery she was given a blood transfusion which was followed by jaundice of less than twenty-four hours duration. Repeated tests of the donor's and patient's bloods failed to show any evidence of incompatibility and no hemoglobinuria was present. Oliguria with increasing nitrogen retention and failure of renal function developed (Table 49) followed by increased

found completely free from protein

In all 3 cases the clinical picture was such as to suggest surgical obstruction of the urinary tract and cystoscopic examination with catheterization of the ureters was performed in each case with negative results.

TABLE 49—CASE 3

Day postpartum	Urine					Blood chemistry mg. per 100 cc.		Blood pressure
	Volume cc.	Specific gravity	Albumin	R B C	Urea per cent	N P N	Creatinine	
1	425	1008	+	+				
2	160							
3	320							
4	410	1005	.					110/70
5	380					104	4.6	
6	450					91	4.9	120/75
7	540	1008	+	+	0.21			
8	1020				0.23	67	6.0	135/70
9	1630		+		0.22			
10	2550				0.23	80	6.4	
11	3500				0.25			150/70
12	2600				0.20			154/75
13	2900				0.29	83	5.4	130/70
14	2370				0.40			
18	1740					71	1.9	105/70
25	1800	1014	Faint trace	0		42	1.4	110/70
30	1300	1020	Faint trace	0		27	1.4	110/70

These 3 cases, in common with those which the author has been able to find in the literature present a distinct clinical picture. Out of altogether 41 observed instances (26 including the author's, reported since 1920), 33 occurred in women, 5 in males and 3 in children. Among the 8 cases not occurring in women, 1 instance followed diphtheria and 3 dysentery. In all women the condition was connected with pregnancy, in 3 instances with miscarriage as early as in the fourth month, once in the fifth month, in the remainder later, usually near or at full term. Fourteen times the pregnancy was complicated by retroplacental hemorrhage. Convulsions occurred in 11 instances, either before, during or after the delivery, in 1 case as late as on the seventeenth day. In the author's first case where in the thirteenth pregnancy abortion took place in the third month, and in the fourteenth pregnancy miscarriage in the sixth month, the heart, at autopsy, proved hypertrophic.

the duration of at least a couple of weeks. In 15 instances, edema of greater or lesser degree preceded the onset of urinary suppression. With these exceptions, there may be absolutely no clinical signs or history to suggest renal involvement or toxemia beforehand. The anuria in the majority of cases was almost complete, coming on





their pycnotic nuclei occasionally visible. The glomeruli, distended within the capsules, enclose fading shadows of red blood cells, leukocytes and detritus. The intralobular arteries (Gross?) are dilated and thrombosed by agglutinated red and white blood cells within a fibrin network, the process can be traced into some of the afferent glomerular vessels and even into the capillary loops themselves. The larger interlobar arteries were free and contained no agglutinated blood cells in the first case, while in the second case the arteries at the cortico-medullary boundary were involved in the process.

2 A second zone, not sharply differentiated from the first, presented similar necrotic areas, but was further distinguished by

chyma). There were also blood extravasations into the interstitial tissue spaces.

In the author's first case these two zones were further characterized by a unique heavy lipoid infiltration, almost wholly confined to the vascular channels of the cortex. The fat was present as

in the tubules—in short, the picture of a severe acute or subacute nephritis. Occasional groups of necrotic tubules were scattered here and there. The medulla was moderately edematous, with irregular streaky tubular and intertubular hemorrhages and abundant casts in the tubules, chiefly hyaline, but also cellular.

**Etiology**—This renal condition has usually been interpreted as a thrombosis of the glomerular and interlobular arterial vessels with consequent necrosis of the infarcted tissue, the thrombosis being ascribed to spasm of all the vessels of the area secondary to some unknown cause. It is difficult to understand a spasm of such long duration and the infarcted tissue is too greatly engorged with blood to fit in with such a long-continued spasm. On the other hand, it would be difficult to account for those cases which have recovered

outcome

According to Ricker and his co-workers<sup>24</sup> the terminal vascular

segments respond to weak irritation by vasodilatation to medium irritation by vasoconstriction and to strong irritation by vasoparalysis the proximal arteries in this state still being constricted while the terminal arterioles and capillaries are greatly dilated. With an increasing degree of the last state there is exudation of serum and leukocytes or even actual hemorrhage by diapedesis and finally complete stasis in the terminal segments (capillaries and arterioles). These observations have been confirmed repeatedly in Professor Oertel's laboratory.

The study of the various zones in the kidney described above shows areas corresponding to these different states of vascular irritation. If the blood stream be in a state of stasis for a sufficiently long period thrombosis will occur particularly in conditions such as pregnancy where there is a decreased coagulation time and increased sedimentation rate. On the other hand if the irritation be removed soon enough the tone of the terminal vascular segments is recovered and a normal blood flow is restored with recovery of the tissues.

What the actual cause of the vascular irritation may be is open to conjecture but it is in all probability bound up with the irritability of the vascular system which has been shown to be present in pregnancy and in some infectious diseases.

## ADDENDUM

Since this communication was prepared in its original form the author has seen and diagnosed during life 2 additional cases of this condition both of which were confirmed at autopsy.

The first occurred in a primipara who suffered a retroplacental hemorrhage in the seventh month followed by anuria of seven days duration. This patient was seen in consultation at another hospital and no studies were made other than to determine the non protein nitrogen which was at the level of 218 mg. per 100 cc.

At autopsy the lesion was found to be apparently earlier than those seen in the other cases consisting of numerous large areas of necrosis confluent in some regions grossly discrete in others but limited to the cortex and otherwise resembling the previous cases both grossly and microscopically.

The second case occurred in a woman aged thirty years who suffered a retroplacental hemorrhage in the seventh month of her fourth pregnancy. In the sixteen hours following delivery 65 cc of urine were recovered by catheter complete anuria ensued for the next thirty six hours after which secretion gradually commenced. Death occurred on the tenth day postpartum during this period a total volume of 900 cc being secreted. (A summary of the urine volume and blood chemical findings is included in Table 50.)

TABLE 50

Day post partum	Urine		Blood chemistry mg per 100 ml		
	Volume	Specific gravity	NPN	Creatinine	Inorganic phosphorus
1	65				
2	0		54.6	2.9	
3	15		109	3.6	7.1
4	40	1.017	136	5.4	
5	67	1.012	150	6.6	3.3
6	110	1.011	160	7.7	
7	135	1.011	180	8.8	4.0
8	184	1.01	160	11.5	
9	243	1.012	178	12.0	1.9
10	105	1.012	18	11.5	5.4

In the microscopic examination of the urine abundant pus cells were found and also an occasional erythrocyte there were no casts. Retinal hemorrhages slight in extent developed two days before death which occurred as in the other cases with no frank signs of uremia.

In view of the author's theory that the condition is due to vasoparalysis of the terminal vascular segments an attempt was made to overcome this state by hypodermic injections of 0.5 cc of adrenalin chloride solution (1 to 1000) these were followed by transient rises of the blood pressure from the average of 140 systolic and 70 diastolic to a maximum of 200/120 with little apparent effect good or bad.

The pathological picture in this case resembled closely that of the first 2 with well marked cortical necrosis grossly and microscopically.

It is possibly of interest that Case 3 who recovered is still alive and now four years after the acute condition she has a normal renal function and blood pressure. There have been no subsequent pregnancies.

In a recent paper Ash<sup>1</sup> has been able to add to the number of cases found in the literature by the author and in addition reports 2 cases of his own occurring in males in which the typical lesion was found at autopsy.

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## CHAPTER XXV

### RENAL NEOPLASMS \*

By STANLEY P. REIMANN, M.D.

#### GENERAL CONSIDERATIONS OF NEOPLASMS

KIDNEY tumors, like tumors in other situations, demand classification, which is ordinarily done either in anatomical terms relating to adult or embryological anatomical situations, or on the basis of morphology. As in congenital anomalies, it is possible, however, to add certain dynamic concepts which help clarify some of the inherent contradictions that no amount of words or classifications or reclassifications in the purely anatomical sense will settle.

It seems better, for the purposes of this chapter, to develop parts of this dynamic point of view and attempt to apply it to renal tumors rather than to describe in detail their morphology and other characteristics which are described in many other places.<sup>1</sup>

By dynamic concepts in this case is meant application in theory to human tumors of certain fundamental ideas concerning what

1. . . . . had better be

been used in the majority of cases as the means by which the evolution of animals and plants has been accomplished it is nevertheless not the only method that has been employed. The group siphonaceous algæ may be mentioned as a class of organisms which have evolved as one gigantic cell, or, by way of the plasmodium route, as it is called.<sup>2</sup>

Thus in considering tumors in general, we are confronted with the problem of what protoplasm can and what it cannot do, what it does and what it fails to do. Of course in humans, we must deal primarily with this protoplasm as it is subdivided into cells though plasmodia are also found in humans. The heart muscle develops as a syncytium there is a syncytium in the decidua, and examples are not rare of tumors that take the character more of a plasmodium than of a cellular structure. With this reservation then, we will proceed to a few pertinent considerations of cells in their relation to tumor formation.

\* From The Laekenau Hospital Research Institute Philadelphia Pa

We may begin by repeating the well known but nevertheless remarkable fact that given the proper environment the fertilized ovum of any species will develop into an end product closely resembling its parents. Furthermore it may be prophesied that given thousands of developing embryos of any one species under the same environmental conditions all of them will approach quite closely the average at any one time (except for occasional mutations).

Even in organisms which never stop growing *i. e.* never reach adult size so to speak—and the majority (in point of number) never stop growing—growth continues differentially in an appointed manner. Thus a lobster of 20 pounds weight is built proportionately like a lobster of 5 pounds weight. In those that do reach and maintain an adult size such as humans what growth occurs then is usually of local parts or systems and is in response to the needs of maintaining the organism as a whole against physiological needs wear and tear injuries etc.

It is obvious that there is *order* in development in any and all stages. Without entering further into a discussion of this phase it may be stated that these considerations can be built into an organismal philosophy for *Nature* in its entirety recognizing among other things that no organism or entity is merely a sum of its parts. From which it follows that no matter how finely the parts of an organism are analyzed a complete picture cannot be obtained without a synthesis of all the parts and then of their interworkings into a whole. The pathological appears when parts do not fit into the *whole* and it is just such a phenomenon which appears in tumor formation as far as we are able to see at present.

The means by which this occurs is by distortion of at least two

multiplication of cells. Differentiation is a broad term meaning numerous things at the present moment it means those changes within a cell which turn it into the more specific from the more general. Later in discussing a special phase the term will be restricted and redefined. Organization means the harmonious co-operative development of cells of various differentiations so that they can function into the frame of a whole. Obviously the factors which determine differentiation and organization come from parents that is cells differentiate and organize true to their lineage whenever they proliferate.

The cells of all tumors proliferate but they differentiate poorly and never organize as do normal cells. Since neoplastic cells with their disorderly differentiation and organization often grow side by side in the very same environment with cells which exhibit

these properties normally, it would seem that the potencies of differentiation and organization are at fault within neoplastic cells.\*

To turn to another phase, it is almost certain that when an individual cell reaches a certain point in its differentiation it loses the power of multiplication. The term "differentiation" is now defined as follows: Differentiation is the result of that series of changes occurring within the protoplasm of a cell which brings it to the point where it is able to perform its function as a member of an adult organism.

If, then, the statement is true that fully differentiated cells in the sense stated above do not differentiate and with it the power of cell division. From this it follows that if interrupted cell multiplication takes place there must be present spare parts, so to speak, from which the new multiplication can occur, or that cells in any given organ or part which retain the power of multiplication for whatever reason (physiological increase in number, repair, regeneration, etc.) are not fully differentiated.\*

It is needless to say that this is an extraordinarily difficult statement to prove if for no other reason than that accurate quantitative measurements of degrees of differentiation of cells are still to be made. But from the general finding that it is among anatomically

cells can divide. At any rate the first step in investigating this

Inherent in this question is also that of dedifferentiation.

seems unlikely. It is not more probable that when a cell differentiates the cells in the dedifferentiated tissue are not those that were previously present, but are new cells which have either failed to differentiate or have differentiated in another direction.

This latter thought introduces considerations of cell potency as of fundamental importance. We say that the fertilized ovum is the cell of the adult organism are another of the potencies is expressed the number

left possible of expression is diminished, but probably never below 2

\* Carried to its logical conclusion this suggests that evolution from the general to the special has not ceased. But who will say that evolution is completed?

As a specific instance, when the cells in the outer layer of the skin are shed, and their place is taken by new cells supplied from the basal layer, are these newly formed basal layer cells capable of turning into only an epithelium similar to the one shed, or have these basal layer cells several potencies? The question is answered thus far in one direction namely, that several potencies are present and which is expressed is determined by the environment in the broad sense of this term, so as to include extraneous factors and the influence of surrounding cells and tissues. As an example of this idea, Wolbach and Howe's experiments may be cited.<sup>4</sup> In animals fed on diets deficient in vitamin A, the cylindrical epithelium of the trachea and other regions is replaced by stratified squamous epithelium, this in turn to be replaced by the normal lining when vitamin A is again supplied in the food. A similar phenomenon is observed in the restoration of normal expression of cell potencies in rickets. Furthermore regeneration as exemplified in the regrowth of claws in crabs and other animals etc., also brings out the fact that protoplasm has more potencies than are usually expressed in a normal individual. Even in mosaic ova some degree of adjustment is possible, while in developing regulatory ova as many as 11 larvae can be developed from 1 egg by suitably severing the cells as they are produced.<sup>5</sup>

The large question in neoplasia is not how many potencies are present in the division-capable cell, or cells from which the tumor arises and continues to grow but what is their quality for this determines whether or not they are to be a neoplasm or will differentiate and organize normally. Smaller questions, mainly in morphology, concern themselves with the number of potencies, for the more that are present the more the tumor is likely to be of the

surrounding tissues. Furthermore, since differentiation and espe-

adult organism in which they happen to occur, the rate of growth of early embryos being tremendously faster than that of older ones, it would seem that the rate of proliferation of neoplastic cells should be in direct proportion to the degree of disturbance of

of great practical importance \*



Finally genetics supplies us with the fact that the incidence of tumors can be increased by inbreeding even though the details of how this increase in susceptibility is transmitted are still in process of study.

To summarize in relation to renal neoplasms It need not surprise us

1 That the less their cells are differentiated and organized the more rapidly they grow

2 That with the kidney developing embryologically from nests of cells with potencies for producing many structures tumors should occur in the kidney anatomically resembling structures in the neighborhood e.g. hypernephromas

3 That attempts at regeneration should often fail in their purpose for to regenerate an entire functioning renal unit requires that vessels glomeruli and all the tubule parts should be reconstructed and then joined to an outlet into the pelvis of the ureter

4 That nodules called adenomas should be relatively common for in many cases they are probably caused by attempts at regeneration

5 That many tumors should be composed of embryonal cells growing in masses utterly unlike any normal structure This brings the opportunity of again condemning the word embryonal in relation to the cells of a neoplasm Embryonal cells are cells with normal potencies not yet expressed neoplastic cells have altered potencies When cells with normal potencies are prevented by the environment from properly expressing them the result is an anomaly or an Albrecht hamartoma

6 That the metastases of many renal tumors should be rapid and widespread For metastasis occurs because the brakes to proliferation i.e. differentiation and organization are disturbed and the more complete the disturbance the more rapid the proliferation i.e. brake relaxed on their expression for totipotentiality (?) or potencies altered (?) Many renal tumors are composed of poorly differentiated and utterly unorganized cells

7 That some renal tumors show adeno formation others papillary structures others squamous cell like arrangements and even especially from the pelvis of the ureter cornifying squamous cell growths That is to say metaplasia is the expression on the part of a cell of a potency other than the normal for the part

8 That more renal tumors may develop in some human families than in others even though the details are in controversy

It remains to tabulate the main forms of renal tumors referring the reader to the standard texts for various details

## GENERAL CHARACTERISTICS OF MALIGNANT RENAL TUMORS

and even into the heart itself. Occasionally the renal vein is completely occluded whereupon infarction of the entire mass occurs. Metastases are often early and widespread because of this tendency to invade vessels. Skeletal metastases may be the first symptoms. In a case observed in a boy aged fifteen years a nodule was removed from the upper right eyelid by an ophthalmologist. Pathological diagnosis was hypernephroma whereupon examination of the child's abdomen disclosed a mass in the right renal region which subsequently proved to be hypernephroma. Invasion into the ureter obstructs this passageway with subsequent hydronephrosis pyonephrosis or complete atrophy of what secreting units remain. Invasion downward and appearance at the ureteral orifice in the bladder is also not uncommon. In a recent case observed a papillary carcinoma was found in a removed kidney. Two years later urinary complaints led to cystoscopy whereupon a fungoid mass was seen protruding through the ureteral orifice on the side from which the kidney had been removed. This was extirpated and the structures of this and of the original kidney tumor were identical.

### CLINICAL COMMENTS

Large tumors of the right kidney push the ascending colon upward and to the left. Those of the left kidney push the descending colon upward so that it passes between the tumor and the anterior abdominal wall.

In addition to such first clinical symptoms as mentioned above in the form of metastases hematuria occurs in upward of 60 per cent of cases. Local pain and a palpable tumor are next in order.

### THE TUMORS

Benign tumors of many types have been described. The commonest are the so-called adenomas and fibromas both of which are without clinical significance and are regarded by many as stated above as being the results of abortive attempts at regeneration.

Since in the development of the kidney the potencies of some cells include that of the production of smooth muscle as it occurs under the capsule fibrosarcomas also occur. A curious combination of multiple small tumors containing fat fibrous tissue

smooth muscle and vessels in the kidney with rhabdomyomas of the heart and tuberous sclerosis is described

The characteristic malignant tumor of the child consists of rapidly growing bulky highly malignant structures containing both epithelial and connective-tissue elements hence its name adenosarcoma. The connective tissue takes various forms such as the ordinary fibrillar type myxomatous type myomatous type while the glandular elements take on bizarre shapes and are of different sizes. Their origin is in dispute but since some have produced metastases purely epithelial in nature others purely sarcomatous and still others containing both elements it may be stated from the point of view of cellular biology that the epithelium occasionally leads the procession and is followed as an attempt at organization by the connective tissue in others both types develop independently of each other but together in a heterogeneous mass. It has been stated that they arise from very early undifferentiated tissue such as the first mesodermic cells by others that they are derived from cells of the embryonal kidney and thus they are spoken of as malignant nephromas. But in considering these ideas the following two possibilities may be put in the form of a question—do or do not malignant tumors arise in the following two circumstances (1) Mere mechanical displacement of undifferentiated cells and (2) the bringing together in abnormal juxtaposition of cells with two different potencies namely for producing connective tissue and for producing epithelium or is not abnormal mingling alone a cause of malignancy?

The author believes at present that either of the two above-stated occurrences leads to the formation of an anomaly in the sense of hamartoma and not a malignant tumor. That is to say if the internal potencies of the cells whatever they may be are not changed some kind of organization however poor will be accom-

expressed are changed not in degree but in kind from those of their normal neighbors which produce the kidney and other surrounding structures

The characteristic tumor of the adult of middle or advanced age is the hypernephroma. For convenience they are divided into typical and atypical those words referring to (1) arrangement of the cells within the tumor many specimens of which show an attempt at layers as in the cortex of the adrenal and (2) atypical in the sense that no arrangement at all is apparent. The latter also can be distinguished by its invasive tendencies into the surroundings and into vessels

Thus the author has seen typical hypernephromas removed on the diagnosis of renal tumor from the symptom unilateral hematuria. They were encapsulated sulphur yellow rounded or angular with architecturally well arranged cells. The picture has been interpreted as relatively benign as contrasted with others of atypical characteristics.

Doubts are often expressed as to their adrenal like origin. Indeed doubts are again and again expressed as to their specificity some calling them a particular kind of carcinoma.<sup>9</sup> The author believes they must be placed in a class by themselves both on anatomical grounds and because of their invasive behavior. Whether it is necessary for their origin to have special cells present with potencies to produce adrenal like structures or whether ordinary kidney cells retain within themselves hidden potencies for producing them remains to be solved. In either case what potencies are present are qualitatively different than those of the normal cells. As far as their physiology is concerned they at least do not produce the changes in secondary sex characteristics such as are seen in true adrenal tumors. The cells of hypernephromas are often highly vacuolated and contain fat globules and often much glycogen. It would be interesting to know their carbohydrate metabolism in Warburg's sense. It would also be interesting to correlate their well marked tendency to invade vessels with some peculiarity of permeability of renal vessels or susceptibility to enzymes or some peculiarity in the enzymes of the tumor cells themselves etc.

Carcinomas of the kidney take on an adenoid architecture or a papilliferous architecture or no architecture at all. By the latter is meant that nests and groups of cells invade in all directions. The pelvis of the ureter gives rise to papilliferous carcinomas with cells of the transitional type. In addition non-cornifying and cornifying squamous-cell carcinomas are not uncommon. The latter occur particularly when stones are present. While stones but more especially incrustations are not uncommon in carcinomas involving the pelvis the question of whether they are primary or secondary is an individual one. *Clinical symptoms* in certain cases seem sufficient evidence that stones were present for some years before carcinoma developed. Their relationship is of course the old one of chronic irritation plus predisposition. The author has

## PROGNOSIS OF MALIGNANT RENAL TUMORS

sion downward by direct spread and through the lymphatics of the ureter is common, no surgical removal is complete without this structure being also removed

The author has had no experience with radiation of these tumors except as a palliation in extensive deposits

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EDITORIAL

## CHAPTER XXVI

### KIDNEY TROUBLE IN ACUTE LUPUS ERYTHEMATOSUS

By ISIDORE SNAPPER M D

**Symptoms**—The skin disease named lupus erythematosus or as Unna called it *ulerythema centrifugum* is widely known. This affection is characterized by red infiltrated patches situated in the

heal gradually, beginning from the center and leaving an atrophic cicatrization. The lesions are usually localized on the face and scalp, however the hands and mucosæ may also be affected. The disease lasts for years and usually undergoes exacerbations in winter and improvement in summer.

The most typical feature is the localization on the face. There the lesion spreads symmetrically over the cheeks and nose tip whereby the exanthema can be compared to a butterfly or a bat and explains why the name of *vespertilio* is so often used. The scabs and scales of this affection have a characteristic quality. Removing a scale which usually is not very easily done, one may observe that the scale has been fixed at its base in the skin with little thorns; after removal wide and patent follicles become visible.

The name lupus erythematosus is hardly justified because this condition certainly has nothing to do with lupus vulgaris or other tuberculous lesions. No tubercles nor tubercle bacilli are found in the infiltrated skin of the lupus erythematosus. Often tuberculin reactions are negative.

Lupus erythematosus seems to be purely a skin disease about which until now internists have had nothing to say. There is however a variety of lupus erythematosus in which complications of the internal organs develop frequently, i. e. acute lupus erythematosus. It may happen that in a patient with ordinary lupus erythematosus an acute generalization of the erythema suddenly develops. Sometimes the disease is acute from the onset and starts as an acute exanthema. This last variety is called lupus erythematosus acutus demilee.<sup>2</sup> Acute lupus erythematosus displays the following symptoms:

(a) *Skin symptoms* In the really acute cases red patches appear on the face and soon flow together. Sometimes a vespertilio form appears. Very often crusts are formed so that this affection makes the impression of an eczema impetiginosum or of erysipelas bullosum explaining why these patients are often sent to the erysipelas wards. Afterwards patches appear on the back of the hands and feet sometimes on the trunk. Especially on the hands these patches may show characteristic properties of the lupus erythematosus lesion because of the atrophic centrum. The lupus erythematosus often spreads to the gingiva causing an ulcerous gingivitis without typical appearance. It must be maintained that the diagnosis of acute lupus erythematosus may be difficult because non typical lesions vesicles and hemorrhagic blisters often develop on the skin.

(b) *High fever*

(c) *Kidney symptoms*

(d) *Often bronchitis and pneumonia*

(e) *Sometimes endocarditis or peritonitis*

(f) *Swelling of glands in axilla or (and) neck*

**Incidence** This disease is most frequent in women. In 1923 only 3 cases of acute lupus erythematosus in males were reported.

**Etiology**—So far as the etiology is concerned different opinions prevail. It has been connected with (a) tuberculosis (b) streptococcus sepsis (c) special granulomatous degeneration of the lymph glands.

From the standpoint of the author the disease is connected with acute inflammation of the kidneys. Here the author wishes to point out the frequent association with inflammation and degeneration of the kidney. Two cases he observed personally showed an insufficiency of the kidney as the outstanding symptom. This caused him to look up the record of 4 other cases which had also been observed in Amsterdam. In these 4 cases kidney symptoms had also been observed.

**CASE HISTORIES** CASE 1—A Male. Admitted June 1 1929. The patient had been under the care of a skin specialist for three weeks for

as a typical brownish evanthesma

alvarsan glycerin the general  
ylate injections resulted in no  
) 9 No autopsy  
years Entered the hospital  
he last six months For three

months she had had high fever and skin affection which started at the tip of the nose and afterwards appeared on the hands fingers and toes

On admission she had butterfly exanthema on the face There were scabs on the tip of the nose finger tips and toes raw underneath, evidently open blisters Her lips were swollen

There was a fine tremor in the muscles of the face, tremor and clonic contractions were present in the hands

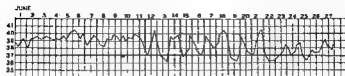


FIG 91 —Temperature record of Case 1

Urine Albumin 0.3 per cent many white blood cells some red blood cells, a few casts

Blood : red 30 per cent

on the fingers and toes

per cent Blood pressure,

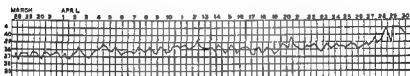


FIG 92 —Temperature record of Case 2

CASE 3 —S H Female aged twenty years Admitted November 11, 1920 She had been healthy until five weeks previously At that time symptoms began with fever chills and headache After two weeks red

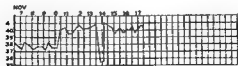


FIG 93 —Temperature record of Case 3

Urine Albumin +++ red blood cells +++ granular casts, +++ Blood pressure 100/60 For a few days before death, diarrhea Death, November 18 1920

Autopsy Bronchopneumonia left lower lobe Right lung small patches of bronchopneumonia Spleen enlarged, 215 gm, liver, 1600 gm,



rash began on hands afterwards on face. She had had fever for six weeks. At the time of admission she had scales on the scalp and red patches on both arms and right knee pneumonia of the lower lobe multiple abscesses on the trunk and thighs hemorrhagic stomatitis

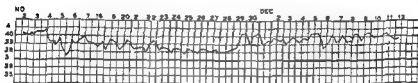


FIG 94 Temperature record of Case 4

Urine Albumin 2 per cent red blood cells + white blood cells + granular casts +

Death December 12 1929

liver lobes mesenteric and

300 gm Microscopic At the time of death there were some conglomerations of mononuclear cells with hemorrhages there were some conglomerations of mononuclear cells no acute or chronic glomerulitis no proliferations of interstitial tissue tubules show autolysis cloudy swelling of the cells of the tubuli contours still visible

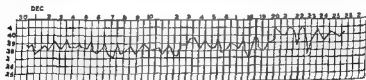


FIG 95 —Temperature record of Case 5

CASE 5—D Male aged eighteen years Admitted November 30 1925 The patient had had rheumatism for five months for four months he had had tenderness and swelling of all joints and rash on the upper lip and chin The rash started on the upper lip and spread like a butterfly over cheeks nose and eye-brows

On admission, he also had red patches with central atrophy on the tips of the fingers and toes right and left pleurisy heart enlarged with presystolic murmur

Urine Albumin ++ red blood cells ++ white blood cells ++ hyaline and granular casts +++

Blood pressure 190/110



liver normal Kidneys macroscopic Kidneys are somewhat enlarged

gouty the red and white blood may be seen in the tubules casts slight increase of the interstitium with edema



FIG 96

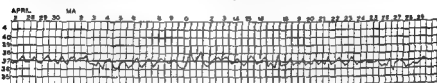


FIG 97



FIG 98

FIGS 96 97 98 —Temperature records of Case II

**Treatment**—All 6 cases died proving once more that in this condition therapy is of no avail. However some of the published cases have survived. Several authors therefore have advocated different treatments: (a) Cacodylate injections intravenously (b) quinine injections (c) roentgen ray irradiation (d) blood transfusion. In the author's patients therapeutic measures have had no beneficial effect.

**Kidney Lesions**—These 6 cases show that acute lupus erythematosus usually presents itself as a septic condition in which the typical lesion of the skin can be found. No endocarditis was present in

or subcutaneous  
os 3 and 4

were not so severe as might have been expected considering the symptoms during life. In the 2 other cases which came to autopsy Nos. 5 and 6 clear-cut kidney lesions were present.

Evidently tuberculosis does not seem a probable cause for acute lupus erythematosus as in only 1 of the 4 autopsies recorded here were signs of active tuberculosis found. Swelling of glands was

present, but swelling of glands cannot be considered as a specific disease

The most remarkable case is the sixth patient in whom the symptoms of nephritis were discovered before the skin symptoms started. The patient entered the hospital because she suffered from nephritis and from fever, probably caused by bronchopneumonia. In the hospital the skin symptoms developed. At first they made a non-specific impression, and only in the long run could the dermatologists be convinced that acute lupus erythematosus was really present. Remarkably enough, the fever subsided one and a half to two months after the skin lesion developed and the patient maintained normal temperatures for two months, although she had typical symptoms of acute lupus erythematosus. She died of renal insufficiency.

These 6 cases show again that there must be an intimate connection between acute lupus erythematosus and nephritis; however, the real reason why acute lupus erythematosus is so often complicated by nephritis remains just as mysterious as all the other complications of this remarkable disease. Perhaps the solution of this problem can be furthered if all cases of acute lupus erythematosus be considered as patients with a general disease. Functional examination of the kidneys of these patients even though they do not show salient symptoms of nephritis will certainly give important results.

TABLE 51.—SUMMARY OF SIX CASES OF LUPUS ERYTHEMATOSUS

	Urine				Blood urea mg %	Blood pressure in Hg	Blood cul ure	Autopsy
	Alb	RBC	WBC	Casts				
♂ K	0.4%	++	++	++	25	140/95	Neg	
♀ D B	0.4	+	++	++	80	160/90	Neg	
♀ Tr	0.1% 0.0%	+	+	+++	?		Neg	Parenchym degeneration tubulointerstitial Glomerulitis acute
♀ H	+++	+++	++	++	100	10/80	Neg	Glomerulitis acute
♂ D	+++	+++	+++	+++	?	160/100	Pneumococcus 2 days before death	Glomerulitis hemorrhagic nephritis parenchymatous
♀ J D	0.13 1.2%	+++	++	+	150	10/170 65/110	Neg	Glomerulonephropathy chronic

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# PART IV

## ALBUMINURIA AND EDEMA

### CHAPTER XXVII

#### MINIMAL ALBUMINURIA AND TESTS FOR ALBUMIN IN THE URINE

By THOMAS B. MAGATH, Ph.D., M.D.

**General Considerations** Tests for the presence of albumin in the urine are given in all laboratory manuals. Compared with most tests of every-day use these give the impression of extreme simplicity. Yet they may be discussed with advantage. Practically the tests for albumin are the most direct tests based upon the visual demonstration of the precipitated protein while theoretically the two problems involved the denaturation and the solubility of proteins constitute intriguing chapters of colloidal chemistry. It is frequently said that no other single laboratory procedure is of greater clinical value than the albumin test. It is important to realize that with the organization under which medicine is practised today especially in the United States most urines are analyzed by technical assistants and not by the responsible physician himself. The isoelectric point of the proteins is nothing but Arabic to most technicians and it would be a mistake to expect these faithful helpers to know that when the urine is

margin of safety in the performance and interpretation of the tests for urinary proteins. On a moment's reflection nobody will gain say the statement that there is a greater assurance of a correct result of a blood sugar determination than of a heat test or Heller's test. In the more complicated blood sugar determination every step is precisely described and the personal equation almost eliminated. Not so in the older and dominating tests for albumin. The answer as to reliability here to be given consists of a comparison of several tests.

From a physiological and clinical viewpoint the problems are two namely the degree of sensitiveness and the pathological significance of minute amounts. The answer to the latter question is of importance in the field of life insurance, recovery from acute nephritis and in essential hypertension. The answer partly depends upon the sensitiveness of the

The sensitiveness of the heat and acetic acid test and of Heller's test is not considered as excessive. It is particularly true that the albumin normally present in the urine for reasons at best partly understood does not render Heller's test positive. Most of our knowledge of the albumin present in normal urine rests upon the work of Morner<sup>12</sup>. By means of a laborious technique starting with dialysis of 1 liter samples this accurate investigator demonstrated the presence of albumin in the urines from 20 men and 22 women all with negative Heller's test. In the urines from 10 men Morner determined the amounts quantitatively obtaining values ranging from 2.5 to 8.9 mg. of protein per 100 cc. Morner considered this protein to be serum albumin. As to the physiological significance of this albumin knowledge is still wanting. One is reminded of Benedict's glucuresis and the name *albumuresis* might not be inappropriate. In regard to glucosuria we know that when it occurs the sugar at once appears in quantities entirely outside of the range of normal glucuresis. Whether the same holds true for albuminuria and albumuresis is not known.

The question arises whether by the use of the more sensitive tests for albumin particularly the use of sulphosalicylic acid one has

Heller's test and on urines the sensitiveness is again three times greater. The conversion of the sulphosalicylic acid test into a quantitative or semiquantitative method might have furthered our knowledge as to the significance of minute amounts of albumin but the reports have not yet been made available. That the danger of introducing too sensitive a test for routine examination has been realized might be induced from the fact that Folin advised a procedure for the sulphosalicylic acid test ten to fifteen times less sensitive than what could have been obtained.

## THE MOST COMMON TESTS FOR ALBUMIN

Before making tests for albumin any urine that is not clear must be filtered or centrifuged. For routine work by technicians all specimens had best be subjected to filtration.

**The Heat Test**—The oldest test used before the days of Bright consisted in heating the urine in a metal spoon the protein if present coagulating at about 55° C and giving a cloudy precipitate. Since most urines are acid it is often unnecessary to add acid to produce flocculation but for alkaline urines proper acidification is necessary.

**Heat and Acid (Acetic or Nitric) Test**—When acetic acid is used one must avoid adding an excess. The common practice is to place about 10 cc. of urine in a test tube heat the top layer over the flame

and add 3 drops of 10 per cent solution of acetic acid By slightly

but if it increases it is due to albumin If the urine is markedly alkaline or rather possesses a high acid-combining capacity as sometimes in cases of nephrosis the prescribed drops of acetic acid may not suffice neutralization becomes necessary before the heating and the addition of the acetic acid Very low salt content of the urine likewise makes flocculation difficult

The test is always accurately done if Sørensen's acetate buffer

To about 10 cc urine in a test tube 1 cc of the reagent is added The whole solution is heated over the flame and boiled for one half minute With fair amount of albumin flocculation occurs directly if less than 0.05 to 0.1 per cent is present an opalescence first develops changing after a few minutes to a fine flocculation On the second boiling the flocculation occurs at once Even with this procedure an alkaline urine has first to be rendered neutral

This test is well discussed by Bang<sup>1</sup> The works of Sørensen<sup>17, 18</sup> are of fundamental importance for its theory

This test is to be preferred to the use of heat and nitric acid If nitric acid is used care must be taken not to add too small an amount else precipitation will not take place It is necessary to add 1 or 2 of urine urine has addition of the acid

A number of substances may interfere in this test nuclealbumin mucin albumoses secondary proteoses and resinous acids excreted after the intake of copaiba cubeb and benzoïn all give some cloudiness The behavior of Bence-Jones protein is discussed in Chapter XXXI

Heller's Test — Although Heller mixed urine and nitric acid the test has survived as a ring or contact test\* The urine is either

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layered on the top of the acid by letting it gently trickle out of a pipette along the wall of the test tube or the acid is layered underneath which is the way usually given in the older literature. A precise method is to introduce the urine into the nitric acid by

The test can be read immediately if a ring or rather a meniscus of protein shows up or after two minutes if the ring is slow in coming. Folin states that it might be read after ten minutes and Morner who did important work on the test read it after fifteen minutes. If the danger in the heat test is that protein present fails to flocculate the danger in Heller's test is that one of the non-specific rings be mistaken for albumin. In concentrated urines rich in ure

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diluted with 1 or 2 volumes of water. The remaining rings form a little above the contact zone. One slightly grayish might form in concentrated urines from precipitation of uric acid as the nitric acid diffuses upward. This too does not occur if the urine is diluted. The other ring is white diffuse in outline and commonly found. According to Morner it is due to condroitin sulphuric acid and usually becomes more distinct when the urine is diluted. Bence-Jones proteins give a typical albumin ring.

The following two tests are based on the ones just described.

**Purdy's Test**—To a test tube two thirds full of urine is added about one-sixth of its volume of saturated solution of sodium chloride and 5 to 10 drops 50 per cent acetic acid. After boiling

stood only practically. The use of Sørensen's buffer solution is more rational.

**Robert's Test** This test which is applied by the ring or contact method has for its reagent a mixture of nitric acid 1 part and biurate 3 parts. It is Bence-Jones protein.

In this test the effect of strong mineral acid on proteins is overshadowed by the effect of concentrated sulphate solutions on protein solubility.



and add 3 drops of 10 per cent solution of acetic acid By slightly

of acid the precipitate was due to calcium ammonium phosphate but if it increases it is due to albumin If the urine is markedly alkaline or rather possesses a high acid combining capacity as sometimes in cases of nephrosis the prescribed drops of acetic acid may not suffice neutralization becomes necessary before the heating and the addition of the acetic acid Very low salt content of the urine likewise makes flocculation difficult

The test is always accurately done if Sørensen's acetate buffer solution is used This reagent which keeps indefinitely is made as follows 50.5 cc glacial acetic acid and 188 gm sodium acetate dissolved and made up to 1 liter The test is carried out as follows To about 10 cc urine in a test tube 1 cc of the reagent is added The whole solution is heated over the flame and boiled for one half minute With fair amount of albumin flocculation occurs directly if less than 0.05 to 0.1 per cent is present an opalescence first develops changing after a few minutes to a fine flocculation On the second boiling the flocculation occurs at once Even with this procedure an alkaline urine has first to be rendered neutral

This test is well discussed by Bang<sup>1</sup> The works of Sørensen<sup>17</sup> are of fundamental importance for its theory

This test is to be preferred to the use of heat and nitric acid If nitric acid is used care must be taken not to add too small an amount else precipitation will not take place It is necessary to add 1 L + meter of urine the the addition of the acid

A number of substances may interfere in this test nuclealbumin mucin albumoses secondary proteoses and resinous acids excreted after the intake of copaiba cubeb and benzoin all give some cloudiness The behavior of Bence-Jones protein is discussed in Chapter XXXI

Heller's Test —Although Heller mixed urine and nitric acid the test has survived as a ring or contact test\* The urine is either

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Secondary proteoses fall out of solution and cause opalescence when the tube cools

A final concentration of the sulphosalicylic acid of 2 per cent is sufficient for complete precipitation of protein. For serial determinations Folin advised the use of 1 cc. of urine in a long test-tube graduated at 25 cc., a 2 per cent solution of sulphosalicylic acid to be added to the 25-cc. mark. Through this dilution the test becomes specific and of reasonable degree of sensitiveness. The standards for comparison devised by Folin corresponded to 0.03, 0.05, 0.1, 0.2 and 0.3 per cent albumin. That the lowest standard corresponded to as high a concentration as 0.03 per cent albumin was significant, the method was devised for use in examinations for life insurance. After several years use of this procedure Kingsbury<sup>11</sup> somewhat altered it and also introduced permanent artificial standards, the basis for them being formazin suspended in gelatin. Kingsbury's alteration represented a swing toward a more sensitive test. He increased the urine to one fourth of the final volume using 2.5 cc. of urine and filling up to a 10-cc. mark with 3 per cent sulphosalicylic acid. Kingsbury's standards corresponded to a protein concentration in the amount of urine used of 0.01, 0.02, 0.03, 0.04 and 0.05 per cent.

All methods so far described have required a minimal amount of laboratory equipment.

**The Scopometer Method** — A more elaborate quantitative method than comparisons with standard tubes is available in Faxon's junior scopometer, an instrument for the measuring of turbidity and colors in routine work. For turbidity measurements Faxon finds it better than the ordinary nephelometer. The phenomenon used in the scopometer is the disappearance of an image in the instrument. The end point in the determination is the vanishing

of a standard target to vanish. For adding density one uses a wedge. The position of the wedge is read off on a scale. The optical density for the different points of the wedge being known, the density of the unknown is obtained and empirically converted into concentration of the unknown. A detailed description of the use of this instrument for the determination of albumin in the urine does not seem to have been published. The method must require that urines that are moderately rich in albumin be diluted in order to obtain a sufficiently stable dispersion of the precipitated protein. For minute amounts in which one chiefly determines the opacity of the wedge, slight variations in the degree of dispersion might greatly affect the reliability.

**Tests With Picric Acid** *Stewart's Qualitative Test*—The reagent for Stewart's test consists of picric acid (wet) 10 gm, magnesium sulphate 400 gm, citric acid 20 gm, and distilled water 1500 cc. The test is a ring test carried out in the usual manner. Stewart claimed that this test was more highly specific and more readily applied than the test by heat and acid.

*Esbach's Quantitative Method*—Esbach's reagent consists of picric acid 1 gm, citric acid 2 gm, and distilled water to make 100 cc. The results obtainable with this well known sedimentation method are of no clinical value in the medicine of today. To obtain the quantitative estimates now desirable the method is too inaccurate.

The following reagents trichloroacetic and sulphosalicylic acid are excellent protein precipitants. They are applied either as contact tests or as turbidity tests. For recognition of minimal amounts the turbidity tests are particularly elegant, the slightest amount of turbidity causing an opalescence which is easily distinguished from a clear control if one looks through the tube longitudinally or in transmitted light. The turbidity tests lend themselves to semiquantitative determinations by comparison with standards of known concentrations.

A trichloroacetic acid concentration of 2.5 per cent in the final solution is sufficient for complete precipitation if the albumin is at all abundant. For minute amounts the test may be arranged so that a final concentration of 10 per cent acid is obtained. For a ring test a reagent has been used consisting of a saturated solution of trichloroacetic acid to which magnesium sulphate has been added to saturation.

Sulphosalicylic acid was applied as a protein precipitant by Roch<sup>15</sup> in 1889 and by MacWilliam<sup>16</sup> in 1891 who in arranging his test even made use of the opalescence produced by minute amounts of protein. The acid has been used in turbidity methods by Kober<sup>17</sup> and by Folin and Denis<sup>18</sup> later by Folin and Benedict<sup>19</sup> by Exton<sup>20,21</sup> and by Kingsbury<sup>22</sup>.

In 20 per cent aqueous solution sulphosalicylic acid is used in a ring or contact test. Urates and resins are not precipitated. Under the name of Exton's test the acid is used as follows: 200 gm of sodium sulphate are dissolved in about 750 cc of water with the aid of heat. The solution is cooled to about 35° C and 50 gm of sulphosalicylic acid are added, dilution with water is made to 1000 cc. Equal parts of urine and reagent are added in a test tube and warmed gently. Boiling is not necessary or desirable. A white cloud shows the presence of protein and the result is read while the fluid is warm, since proteoses cause cloudiness when the liquid cools. The Bence-Jones protein causes a heavy precipitate resembling curdled milk which clears partially or wholly on boiling.

dilutions the use of Sørensen's buffer proved somewhat better than the addition of acetic acid drop by drop the sensitiveness being 1 in 50 000 and 1 in 25 000 to 33 000 respectively. On urines the sensitiveness rose to 1 in 200 000 without any difference between

TABLE 59.—SENSITIVENESS OF HELLER'S TEST ON DILUTE SERUM AND URINE

Protein content Per cent	Test read after min				Material
	2	5	1	30	
0.001	—	—	—	—	Diluted blood serum
(1 in 50 000)	—	—	—	—	
0.003	—	—	—	—	
(1 in 33 000)	—	—	—	—	
0.004	+	+	+	+	
(1 in 25 000)	+	+	+	+	
0.005	+	+	+	+	Normal urine enriched by serum
(1 in 20 000)	+	+	+	+	
0.006	+	+	+	+	
(1 in 17 000)	+	+	+	+	
0.007	+	+	+	+	
(1 in 14 000)	+	+	+	+	
0.009	—	—	—	+	Normal urine enriched by serum
(1 in 12 000)	—	—	—	+	
0.009	—	—	—	+	
(1 in 11 000)	—	—	—	+	
0.010	—	—	—	+	
(1 in 10 000)	—	—	—	+	
0.0125	—	+	+	+	
(1 in 8 000)	—	+	+	+	
0.015	+	+	+	+	
(1 in 6 700)	+	+	+	+	

TABLE 60.—SENSITIVENESS OF TESTS WITH HEAT AND ACETIC ACID SULPHOSALICYLIC AND TRICHLOROACETIC ACID IN DILUTE SERUM AND URINE

Protein content Per cent	Dilute serum				Enriched urine			
	Heat and acetic	Heat and sulphosalicylic	Sulphosalicylic	Trichloroacetic	Heat and acetic	Heat and sulphosalicylic	Sulphosalicylic	Trichloroacetic
0.0001	—	—	—	—	—	—	—	—
(1 in 1 000 000)	—	—	—	—	—	—	—	—
0.0002	—	—	+	+	—	—	+	+
(1 in 500 000)	—	—	+	+	—	—	+	+
0.0005	—	—	+	+	—	—	+	+
(1 in 200 000)	—	—	+	+	—	—	+	+
0.00075	—	—	+	+	—	—	+	+
(1 in 133 000)	—	—	+	+	—	—	+	+
0.001	—	—	+	+	—	—	+	+
(1 in 100 000)	—	—	+	+	—	—	+	+
0.002	—	+	+	+	—	—	+	+
(1 in 50 000)	—	+	+	+	—	—	+	+
0.003	—	+	+	+	—	—	+	+
(1 in 33 000)	—	+	+	+	—	—	+	+
0.004	+	+	+	+	—	—	+	+
(1 in 25 000)	+	+	+	+	—	—	+	+
0.005	+	+	+	+	—	—	+	+
(1 in 20 000)	+	+	+	+	—	—	+	+

## SENSITIVENESS OF THE VARIOUS ALBUMIN TESTS

The sensitiveness of the different tests proves a complicated matter. Concerning Heller's test Hammarsten<sup>3</sup> stated that an amount of albumin of 0.002 per cent (1 in 50 000) is easily detectable and in another mode of expression with negative Heller's test the urine contains less than 0.003 per cent (1 in 33 000) of albumin. Morner<sup>12</sup> found the test less sensitive 0.008 per cent (1 in 12 500). Bang<sup>1</sup> saw in this relatively low sensitiveness an advantage and an assurance that the albumin content of normal urine is not picked up by this test. Bang considers the heat and acetic test to be of about the same sensitiveness as Heller's test.

Two or more questions are involved: (1) What is the minimal amount of albumin detectable by the different tests? This is preferably tested on dilutions of serum with 0.9 per cent sodium chloride solution. (2) Given these amounts of albumin present in urine, how much if at all do other urinary constituents particularly the colloids influence the sensitiveness? Different concentrations surely will have different effects. Different diets too might influence the colloid content of the urine, a point to which little attention has been given. It might be recalled that Folin and Berglund<sup>6</sup> on feeding to a normal person a certain brand of dextrin recovered grams of than maltose. The influence of condroitin sulphuric acid is

(3) When investigating sensitiveness a different care is surely taken in creating favorable optical conditions for the detection of a faint reaction than in routine work, particularly if urines are not examined in series but one by one. How far does this reduce sensitiveness?

Inquiry into Heller's test (Table 52) shows a difference in sensitiveness for the same amount of albumin depending on whether the albumin is in dilute sodium chloride solution or whether it is added to normal urine of medium specific gravity (negative for albumin according to the trichloroacetic acid test). On serum the test was positive in dilution 1 in 25 000, the white ring appeared within two minutes and no increase in sensitiveness took place during fifteen minutes. On urine the sensitiveness after two minutes was 1 in 6700 only, with an increase of sensitivity to 1 in 12 500 after thirty minutes. When the reading was made after five minutes the sensitiveness in diluted serum was 7.5 mg per 100 cc greater than in urine. The role of the condroitin sulphuric acid and other protein precipitants normally present in urine which cause a reduction in sensitiveness will not be further con-

(Table 53) is  
On the serum

dilutions the use of Sørensen's buffer proved somewhat better than the addition of acetic acid drop by drop, the sensitiveness being 1 in 50,000 and 1 in 25,000 to 33,000, respectively. On urines the sensitiveness rose to 1 in 200,000, without any difference between

TABLE 52.—SENSITIVENESS OF HELLER'S TEST ON DILUTE SERUM AND URINE

Protein content Per cent	Test read after in s				Material
	2	5	10	30	
0.002 (1 in 50,000)	—	—	—	—	Diluted blood serum
0.003 (1 in 33,000)	—	—	+	+	
0.004 (1 in 25,000)	+	+	+	+	
0.005 (1 in 20,000)	+	+	+	+	
0.006 (1 in 17,000)	+	+	+	+	
0.007 (1 in 14,000)	+	+	+	+	
0.008 (1 in 12,500)	—	—	+	+	Normal urine enriched by serum
0.009 (1 in 11,000)	—	—	+	+	
0.010 (1 in 10,000)	—	+	+	+	
0.0125 (1 in 8,000)	+	+	+	+	
0.015 (1 in 6,700)	+	+	+	+	

TABLE 53.—SENSITIVENESS OF TESTS WITH HEAT AND ACETIC ACID, SULPHOSALICYLIC AND TRICHLOROACETIC ACID IN DILUTE SERUM AND URINE

Protein content Per cent	Dilute serum				Enriched urine			
	Heat and acetic	Heat and Sørensen	Sulpho- salicylic	Trichloro- acetic	Heat and acetic	Heat and Sørensen	Sulpho- salicylic	Trichloro- acetic
0.0001 (1 in 1,000,000)	—	—	—	+	—	—	—	+
0.00025 (1 in 400,000)	—	—	+	+	+	+	+	+
0.0005 (1 in 200,000)	—	—	+	+	+	+	+	+
0.00075 (1 in 133,000)	—	—	+	+	+	+	+	+
0.001 (1 in 100,000)	—	—	+	+	+	+	+	+
0.002 (1 in 50,000)	—	+	+	+	+	+	+	+
0.003 (1 in 33,000)	+	+	+	+	+	+	+	+
0.004 (1 in 25,000)	+	+	+	+	+	+	+	+
0.005 (1 in 20,000)	+	+	+	+	+	+	+	+

negative and the others positive. The heat and acetic acid test alone was positive in 8 instances. Stewart's test alone was positive 3 times and the sulphosalicylic acid test alone once. Thus these three tests give fairly consistent results.

TABLE 55 COMPARISON OF VARIOUS TESTS ON 100 SPECIMENS OF URINE

Heat and acetic acid	Stewart	Sulphosalicylic acid	Instances of agreement per cent
Positive	Positive	Positive	33
Positive	Positive	Negative	6
Negative	Positive	Positive	5
Positive	Negative	Negative	11
Negative	Positive	Negative	3
Negative	Negative	Positive	1
Negative	Negative	Negative	44
Total			100

Table 56 shows that the presence of leukocytes or pus is connected rather closely with the presence of protein and that when leukocytes were present all of the methods except Heller's test gave a high percentage of positive tests for protein. Slightly more of the urines in which casts are present are positive by the heat and acetic acid test than by any other. Casts were found in 20 per cent of those positive for proteins by this method and in a slightly lower percentage by the other tests. In 4 specimens of urine reported negative for albumin by all tests there were hyaline casts.

TABLE 56 RELATION OF CASTS, BLOOD AND PUS TO PROTEIN (100 SPECIMENS OF URINE)

	Positive protein specimens	Microscopic elements in specimens positive for protein per cent			
		Casts	Blood	Leukocytes or pus	Negative
Heat and acetic acid	48	20	19	94	2
Stewart	48	15	19	88	4
Sulphosalicylic acid	40	11	27	92	0
Heller	7	14	43	86	0
Positive protein*	56	25	16	96	4
Negative protein (all tests)	44	9		98	63

\* Positive by some one test or by more than one.

## SIGNIFICANCE OF MINUTE GRADES OF ALBUMINURIA

Evidence  
of minute  
significance  
this way

in the urine  
This volume contains such contributions by Dr. J. W. C.

McKinlay and 13 Medes Sanford Conner Magath and Heck,<sup>16</sup> in 70 cases correlated the finding of albuminous urine with other significant data. Definite renal lesion was present in 40 per cent while in 30 per cent any lesion remained uncertain. In the absence of an Grade 1 by the Heller's test in 10 of the 70 cases, 10 of the 70 cases were "questionable" cases.

In the group of cases of renal disease albuminuria Grade 1 was recorded in 15, Grade 2 in 6, Grade 3 in 3 and Grade 4 in 2. The changed attitude of the life insurance companies toward albuminuria is significant. Ogden<sup>17</sup> in 1915 made the statement: "Not many years ago insurance was refused any person whose urine contained albumin." At the same time he reported favorable ten years' experiences from the insurance of a great number of individuals with slightest possible trace of albumin. The knowledge derived from the quantitative determinations adopted by a number of insurance companies during the last decade forms the basis for the present mode of action. Albuminuria in amounts up to 0.03 per cent does not prevent a person under thirty-five years of age and with a negative previous history and otherwise normal findings from being accepted as a standard risk. Even persons whose urine contains as much as 0.05 per cent of albumin might under some circumstances be rated as normal risks. Thus the development that has taken place in this quantitative estimates carried out by methods

and in which albumin not detectable by Heller's test was demonstrated by one of the more sensitive methods the individuals were nephritics who otherwise had recovered except for the minimal amount of albumin in their urine and occasional red blood cells in the sediment or they had uncomplicated chronic hypertension. In such cases the sensitive methods add valuable clinical information that otherwise is missed.

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## CHAPTER XXVIII

### ALBUMINURIA IN YOUNG MEN

By HAROLD S. DITTMER, M. A., M. D.

AND

CHAUNCEY A. MCKINLAY, M. D.

**Introduction**—The occurrence of albumin in the urine of sup-

of renal disease. Stirling<sup>19</sup> in 1887 noted the apparent relationship between posture and the occurrence of albumin in the urine of certain individuals. Jassier<sup>20</sup> in 1889 suggested the term orthostatic albuminuria. Since that time numerous studies of this condition have been made and opinions expressed as to its frequency and significance. In this chapter we are presenting the results of some studies of albuminuria in supposedly normal persons carried on in the Student Health Department of the University of Minnesota over a period of several years. The group which has been studied consists of 16,748 male students who entered the University of Minnesota between 1921 and 1928. Tests of the urine were performed as part of the entrance physical examinations. In test-

first examination. Over the seven-year period covered by this investigation the incidence of albuminuria varied considerably from year to year. This difference may have been due in part, at least, to different standards for the interpretation of the test. Attempts were made to prevent this, but inasmuch as the same technicians did not perform these tests throughout the entire period, the possibility of different standards, particularly for minimal amounts, is possible. Ashburn<sup>21</sup> found a considerable variability in the incidence of albuminuria in West Point cadets in certain years and suggests the possibility of epidemics of albuminuria. Evidence supporting this suggestion is not convincing.

Comparisons of this incidence of albuminuria to that reported by others is somewhat unsatisfactory because investigators have used

different tests, the delicacy of which, as Dr Magath pointed out, varies widely. Ashburn gives a report of 5855 routine urine examination on 2269 cadets. Of this number, 7 per cent were reported as positive for albumin. Parmenter<sup>14</sup> reports that over a period of four years 5 to 7 per cent of Harvard freshmen had albuminuria on a single examination. Other writers<sup>7, 9, 11, 15</sup> report incidences of 3 per cent to as high as 60 per cent. This highest incidence was in children from two to six years of age, described by the authors, Calvin, Isaacs and Meyer,<sup>8</sup> as having had "poor care."

**Results of Reexaminations**—Over a period covering the later years of this study, 460 students who showed albumin on the first urine examination were reexamined. One hundred and eleven of these had only one subsequent urine examination, but the others had from two to thirty specimens examined. On the basis of these subsequent examinations the cases were classified as transient albuminuria, meaning albuminuria on only the first examination with later examinations negative, occasional albuminuria, frequent or persistent albuminuria and albuminuria with probably kidney damage. As seen from Table 57 approximately two-thirds of the

TABLE 57—RECLASSIFICATION OF ALBUMINURIA 460 CASES REEXAMINED

	Albuminurias per cent	Total (calculated) per cent
Transient albuminuria	63.3	3.6
Occasional albuminuria	13.0	0.7
Persistent albuminuria	12.0	0.6
Probable kidney disease	6.7	0.4

cases who showed albuminuria on the first examination had negative reports on subsequent tests while only 6.7 per cent had what seemed to be definite evidence of kidney damage. Taking the results of these reexaminations as a basis and computing the inci-

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general disease is still somewhat of a debatable subject. Elwyn<sup>3</sup> states that in all types of albuminuria there is either a deficiency of oxygen supply or injury by a toxin and that in either case glomerular and capsular epithelium are damaged. Russell<sup>16</sup> believes that orthostatic albuminuria is frequently caused by some form of

physical efficiency. Ichle,<sup>10</sup> in his exhaustive study stressed the effect of exaggerated lordosis as a cause of albuminuria. However, the careful observations of Goetzky<sup>7</sup> confirmed by many observers, indicated that as a cause marked lordosis is probably unimportant.

The significance of albuminuria to health has been shown by Dublin<sup>1</sup> and by Palmer.<sup>11</sup> Dublin computed the mortality rate over a period of approximately six years of 5000 persons who were rejected for life insurance because of albuminuria or albuminuria with casts. The mortality rate of persons in the age group fifteen to twenty-four years who showed only a faint trace of albumin with or without casts was no greater than expected but the rate of persons in the same age group who showed a trace or large trace of albumin was from two to six times the expected. Palmer re-examined 35 Harvard graduates who had had albuminuria when examined as students approximately eight years before. In only 1 of these was there persistent albuminuria and in 1 more transient albuminuria at the time of reexamination. Although studies such as these suggest that small amounts of albumin in the urine unaccompanied by other evidences of kidney damage are without significance it seems that further light on this condition may be obtained by a study of the physical and physiological characteristics of a group of persons who have albuminuria.

### STATISTICAL STUDIES OF ALBUMINURIA IN YOUNG MEN

With this in mind three groups of students were compared as to age, height, weight, percentage, pulse-rate, blood pressure, histories of certain past diseases and the condition of the nose and throat. Group I is a control group composed of students with normal urinary findings, each one of which was examined just before or just after one of the students in the albuminuria group. Group II consists of students who had albuminuria on the entrance examination and Group III consists of students with probable kidney disease. The diagnosis of kidney disease in some of these cases was made by private physicians but in the majority of the cases the diagnosis was made by members of the Health Service staff and was based upon urinary findings, chemical tests of the blood and tests of renal function, particularly the phenol-sulphonphthalein test and the various water-concentration and dilution tests. While it is possible that a few students in the albuminuria group may have undiscovered evidence of kidney damage the probability is that the number of these is very small because an effort was made to secure blood chemistry analyses and urinary function tests on all students who showed persistent albuminuria or any considerable number of casts, particularly granular, in the urine. It is possible too that some of the cases classified as nephritis but upon which



of the control group and the albuminuria group are practically identical but the group with probable kidney disease has significantly higher pressures. The percentage of the albuminuria group with blood-pressures of 130 mm or more is significantly greater than the percentage of the control group. When one gets up to pressures of 140 mm or more the difference in percentages between the two groups is not significant. This slight increase in the blood pressure of the albuminuria group probably is evidence of a nervous reaction.

**Diastolic Blood pressure.** The mean diastolic blood pressure of

higher level of pressure.

**Pulse pressure.**—Hanger and Hooker<sup>4</sup> suggest that a diminution of pulse pressure is a possible cause of albuminuria and that the amount of albumin excreted varies inversely to the magnitude of the pulse-pressure. As will be seen from Table 58 a comparison of the pulse pressures of these groups lends no support to this suggestion.

**Summary of Physical Findings.** These points brought out in the foregoing paragraphs are shown even more clearly in Table 59 where the differences between the findings in the three groups are given in columns 2, 3 and 4. In columns 5, 6 and 7 are tabulated the ratios of the differences to their probable errors. As is known, when this ratio is 3 or greater the difference considered from a statistical point of view is held to be of significance.

TABLE 59. DIFFERENCES BETWEEN VARIOUS GROUPS IN TABLE 58 TOGETHER WITH THE STATISTICAL SIGNIFICANCE OF THESE DIFFERENCES.

	Difference			Ratio of difference to its probable error		
	(Control group I)	(Control group II)	(Control group III)	A	B	C
	(Control group I)	(Control group II)	(Control group III)			
Age	+4.0 ± 1.0 1	1.0 ± 0.5	1.0 ± 0.5	4.3	2.1	3.5
Height weight percent age	+4.2 ± 0.0 1	+1.3 ± 0.5	-0.2 ± 0.5	4.6	0.8	0.5
Percent under 90	+1.1 ± 2.10	+3.3 ± 4.0	+0.7 ± 0.0	0.1	0.6	0.5
Percent over 90	+0.31 ± 1.90	+1.73 ± 4.5	+1.4 ± 4.5	0.2	0.4	0.3
Pulse-rate	+4.0 ± 0.3 1	+0.7 ± 1.7	+0.35 ± 1.7	1.1	0.2	0.2
Percent over 90	1.9 ± 1.0	+4.42 ± 5.4	+0.71 ± 5.5	1.1	0.8	1.2
Systolic blood-pressure	+0.14 ± 0.56	10.34 ± 9	-10.74 ± 2.9	0.3	3.7	3.7
Percent over 130	7.30 ± 2.10	-35.47 ± 7.9	35.67 ± 8.0	3.7	4.6	3.4
Percent over 140	2.77 ± 6.1	25.76 ± 9	-2.94 ± 7.9	1.6	3.2	2.9
Diastolic blood-pressure	+1.0 ± 0.47	6.67 ± 9	-7.43 ± 2.9	1.7	1.3	2.5
Percent over 90	+1.15 ± 1.10	-27.4 ± 7.8	24.45 ± 7.8	1.0	3.5	3.6
Percent over 130	-0.4 ± 0.41	16.7 ± 6.6	-16.11 ± 6.2	0.7	2.8	2.6
Pulse-pressure	0 ± 0.3	4.1 ± 1.1	-2.7 ± 1.1	1.3	1.0	2.5

\* Mean

our own data are incomplete, might be questioned. In spite of these possible inaccuracies, for purpose of comparison the groups are relatively satisfactory (Table 58).

TABLE 58 —RELATION OF ALBUMINURIA TO CERTAIN PHYSICAL AND PHYSIOLOGICAL DATA

	I Control group (no albuminuria) 480 cases	II Albuminuria (no demonstrable kidney damage) 455 cases	III Probable kidney disease 17 cases
Age	*19.59 ± 0.09	19.08 ± 0.08	20.88 ± 0.53
Height-weight percentage	*96.15 ± 0.39	93.77 ± 0.35	94.62 ± 1.74
Per cent under 90	26.96 ± 1.40	26.84 ± 1.60	23.08 ± 6.90
Per cent over 110	9.42 ± 0.90	9.11 ± 0.90	7.69 ± 4.40
Pulse-rate	*82.63 ± 0.39	82.00 ± 0.44	82.35 ± 1.61
Per cent over 90	16.18 ± 1.10	18.10 ± 1.30	11.76 ± 5.30
Systolic blood pressure	*123.24 ± 0.40	123.39 ± 0.39	134.12 ± 11.58
Per cent 130 mm +	25.24 ± 1.40	36.04 ± 1.60	64.71 ± 7.80
Per cent 140 mm +	10.04 ± 0.90	12.31 ± 1.10	35.29 ± 7.80
Diastolic blood pressure	*74.21 ± 0.33	73.43 ± 0.33	80.88 ± 2.86
Per cent 90 mm +	7.97 ± 0.80	11.83 ± 0.80	35.29 ± 7.80
Per cent 100 mm +	1.26 ± 0.30	1.54 ± 0.30	17.65 ± 6.20
Pulse pressure	*49.03 ± 0.53	49.95 ± 0.51	53.24 ± 4.06

\* Mean

**Age**—The average age of the control group is about one-half a year greater than that of the group with albuminuria, and the probable error is sufficiently small to make this difference seem significant. Whether this difference in age is in line with the suggestion of Hess<sup>6</sup> and others that albuminuria is more frequent in children and adolescents than in older age groups or whether the difference is a mere chance will require further study. The higher

whom had disabilities of nephritis

**Height-weight Percentage**—The height-weight percentage as here

per cent of standard, however, is approximately the same in the two groups, indicating that the degree of the underweight in the albu-

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makeup. The mean pulse-rate of the albuminuria group is

ings only relatively accurate. For comparative purposes however, they should serve satisfactorily. Instead of attempting to list the various tonsil abnormalities which the nose and throat specialist noted these were all grouped together and the conditions tabulated as tonsils abnormal. The frequency of this condition as shown in the table is practically the same for all groups. Assuming

albuminuria group than in the control group. Additional weight is added to this conclusion by the significantly smaller percentage of 'normal tonsils' among the albuminuria group.

TABLE 60. INQUIRY INTO THE RÔLE OF CERTAIN PREVIOUS OR PRESENT PATHOLOGICAL CONDITIONS

In line per cent of	I Control group no albuminuria 440 cases	II Albuminuria no demonstrable kidney damage 455 cases	III Probable kidney disease 17 cases	Difference Group I minus Group II	Probability of chance difference greater than or equal to actual difference
Serum fever	13.06 ± 1.1	1.34 ± 1.1	23.3 ± 6.9	-1.42 ± 1.60	1 n 4
Rheumatism	5.21 ± 0.7	6.9 ± 0.8	11.76 ± 5.3	1.35 ± 1.10	1 n 6
Diphtheria	6.25 ± 0.7	6.97 ± 0.8		0.12 ± 1.10	1 n 2
Tonsillitis	3.06 ± 1.3	23.80 ± 1.3	17.65 ± 6.2	+0.66 ± 1.80	2 n 5
Frequent colds	16.01 ± 1.1	2.86 ± 1.8	23.41 ± 7.5	-6.82 ± 1.70	1 n 247
Tonsils					
Altered	24.96 ± 1.4	38.24 ± 1.6	29.41 ± 7.5	-9.94 ± 2.10	1 n 1000
Normal	4.42 ± 1.6	31.41 ± 1.6	47.06 ± 8.7	+12.81 ± 2.30	1 n 1000
Abnormal	25.21 ± 1.3	27.47 ± 1.4	23.53 ± 6.1	-2.26 ± 1.90	1 n 5
Chronic nasal discharge	0.42 ± 0.2	.42 ± 0.4		2.00 ± 0.45	1 n 1000

Chronic nasal discharge was the only condition tabulated in regard to the nose. This was chosen because of its possible relation to sinus infection. The incidence of this condition is not great in either group but it occurs significantly more frequently in the albuminuria group than in the control group.

**Discussion and Summary.**—The incidence of albuminuria in 16,748 supposedly healthy freshmen students at the University of Minnesota with an average age of approximately nineteen years was found to be 5.24 per cent. The nitric acid ring test was used in making these examinations and results are based upon the examination of a single specimen. Had multiple specimens from each patient been examined over a period of time or had more delicate tests been used the incidence would undoubtedly have appeared considerably greater. Some writers<sup>16,17</sup> state that it is probable that albumin could be found in the urine of every person if a sufficient number of specimens were examined.

Subsequent examinations were made of urine specimens of 160 students who had albumin on the first examination. A reclassification



A general inspection of columns 2 3 and 4 of Table 59 reveals the fact that the differences between Groups I and II i e the normal subjects and those with albuminuria are in most cases relatively slight as compared with the differences between either of them and Group III the values in columns 3 and 4 being of approximately the same order This indicates that the normal subjects and those with albuminuria tend to resemble each other more closely than either resembles the group III. This is especially true in the case of the normal subjects.

The only statistically significant (column 5) aside from the age factor which has already been discussed are the height weight percentage and the significantly greater number who have systolic pressures over 130.

Both Groups I and II are statistically different from Group III in regard to mean systolic blood pressure and the relatively lesser number having pressures over 130 and over 140 mm Hg. The differences in the diastolic blood pressures on the other hand are not significant.

GROUP I OR GROUP II Here again the differences in the diastolic pressures are not extreme as indicated by the lack of statistically significant difference in the percentage with pressures greater than 100 mm Hg.

## RELATION OF ALBUMINURIA TO OTHER DISEASES

**Past Diseases and Frequent Infections**—The frequency of the history of several diseases which seemed most likely to have some relationship to albumin in the urine were compared and these comparisons for the groups are displayed in Table 60. Scarlet fever shows increased incidence only in the group which has definite kidney disease. The incidence of diphtheria is practically the same in all groups but a history of rheumatism is given significantly more frequently by the group with probable kidney disease.

**Frequent Illnesses**—On the history blanks students report as to the frequency with which they have various symptoms illnesses etc. Attacks of influenza are considered to be related to kidney disease approximately equal frequency by all three groups. Frequent colds on the other hand show a significant relationship to the occurrence of albuminuria.

**Condition of Nose and Throat** As part of the entrance physical examination the nose and throat of each student is inspected by a nose and throat specialist and the report of the condition observed is recorded. These examinations are hurriedly done and the find-

10 JENLE L 1914 Die Albuminurie Mensch und experimentelle Beiträge zur Frage der orthostatisch lordotischen und der nephritischen Albuminurie

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13 PALMER R ■ 1931 Functional albuminuria J Am Med Assn 96 1559-1562

14 PARMENTER, W C 1930 Observations on the significance of functional albuminuria in young men at Harvard University Boston Med and Surg J 183 677-681

15 RUSSELL, J W 1925 The origin and significance of postural (ortho-

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20 TEISSIER, J L 1899 Albuminurie de la station debout albuminurie orthostatique Semaine méd 19 415-427

21 THOMP E C AND WAKEFIELD E C 1933 Orthostatic albuminuria a comparison with other types of albuminuria Ann Int Med 6 1565-1578

tion made from the results of these later examinations showed that 68 per cent had only transient albuminuria 13 per cent occasional albuminuria 12 per cent frequent or persistent albuminuria and 7 per cent probably kidney disease

types however is indefinite and every examiner finds numerous cases which do not seem to fit into any of these categories

The etiology of this type of albuminuria in healthy persons is not clear The upright position and physical exercise are undoubtedly factors in certain cases Constriction of the renal vessels<sup>18</sup> through the injection of adrenalin and emotional excitement have been shown to produce albuminuria in experimental animals In humans similar factors may be operative our findings show that a

Certain writers suggest that this type of albuminuria is a stage in the recovery of an inflammatory process of the kidneys such as occurs in acute tonsillitis but related to a low colds diseased

The determination of albuminuria will necessitate still further study but although this analysis shows that students with albuminuria are but little inferior physically to those whose urine contains no albumin it would seem as stated by Thorp and Wakefield<sup>21</sup> that the burden of proof rests with those who do not consider it due to renal injury

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1157-1160

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21 THORP, F G, AND WAKEFIELD, I G 1933 Orthostatic albuminuria, a comparison with other types of albuminuria. Ann. Int. Med., 8 1565-1578

## CHAPTER XXIX

### ORTHOSTATIC PROTEINURIA \*

By GRACE MEDES, PH D AND MARY NEEMES, BS

#### ETIOLOGY OF ORTHOSTATIC PROTEINURIA

SINCE 1870, when Ulzmann<sup>25</sup> reported 8 cases of proteinuria which could not be considered pathological, at least four general theories have been advanced to explain the predominant etiological factor in the so-called occasional or harmless proteinurias (1) Sub-normal vascular development, (2) vasomotor instability, (3) general lowered condition, especially undernourishment and chronic infection, and (4) lumbar lordosis causing renal venous stasis. That the kidney is not necessarily impaired is now generally accepted, nevertheless borderline cases are frequently reported and the question has remained unanswered as to whether or not there may be a gradation from harmless proteinuria to mild chronic nephritis. The present study is an attempt to throw light on this point.

No small part of the confusion in regard to the subject of harmless proteinuria seems to be due to the indiscriminate use of the large number of descriptive names applied to these proteinurias and the consequent assumption that they have a common etiology. To recount a few such descriptive terms in general use, we have

(Dubreuilh<sup>3</sup>) and albuminuria of adolescents (Moxon<sup>4</sup>), although it was already known that protein might appear in the urine of healthy persons under certain special conditions, such as after cold baths and after violent exercise (Mahomed, quoted from Moxon).

Teissier<sup>28</sup> first used the term *orthostatic albuminuria* for proteinuria which appears when the subject is in the upright position, and Jehle,<sup>11</sup> in an exhaustive investigation demonstrated that in his cases these proteinurias were associated with chronic or assumed lordosis. Nassau<sup>17</sup> recognized two types the *true lordotic* and a second which he called *orthotic*, following the terminology of

\* Aided by grants from the Research fund of the Graduate Medical School of the University of Minnesota.

Heubner,<sup>8</sup> wherein the proteinuria occurred in the upright position unassociated with lordosis. Other investigators (*e. g.*, Post and Thomas<sup>10</sup>) have described a third type in which the proteinuria is

reappear. He finds this type frequently following upon severe infections and it seems probable he is dealing with mild cases of nephritis in which the protein appears in the urine only when the subject is in the upright position. A study of this group rightfully falls in the field of nephritis and possibly represents an extremely mild primary attack of nephritis in process of clearing up or of passing over to a latent period and characterized by an orthostatic proteinuria as the only sign.

As early as 1878 Leo<sup>7</sup> suggested vascular asthenia as the cause of occasional proteinuria, to explain its appearance in his patient after exercise and its disappearance after rest in bed or intake of food. Following the frequent observation beginning with Clark<sup>2</sup> that alkalization of the urine decreases the output of protein in

cases. It is impossible even to cite all the attempts to explain the various orthostatic proteinurias on this basis. Post and Thomas, who first crystallized the idea, believed failure to excrete protein upon alkalization to be characteristic of all non-nephritic cases and even suggested that the response to alkalization might be made the criterion for differentiating them from the nephritic type. By this test it may be possible to demonstrate a gradation from one to the other since Nassau<sup>1</sup> found in his studies that in the orthotic cases a much greater amount of alkali was required to decrease the output of protein than in the true lordotic type.

Unger and Hooker<sup>4</sup> and Hooker, Huggan and Zartman<sup>11</sup> demonstrated that in their cases of orthostatic proteinuria the amount of protein excreted in the urine varied inversely with the pulse pressure. Birch, Boyce and Savage<sup>5</sup> found that the proteinuria exhibited by Marathon runners coincided in time with the post-exercise fall of pulse pressure and disappeared with the return of this factor to normal. Helkbrandt, Brogdon and Kelso<sup>6</sup> in a

authors found other instances of occasional proteinurias which followed violent and rapid muscular exercise but which were not related to variations of pulse pressure. They explained these findings on the hypothesis that exercises of speed also bring about generalized systemic increase in acidity, altering the permeability of the renal cells to blood proteins in consequence of which albumin appears in the urine. This explanation is essentially similar to that of Jervell<sup>1</sup> who explains the proteinuria following severe exercise by stasis and lactic acid accumulation. He states that with a lactic acid content in the blood of more than 75 mg per 100 cc after physical exertion he always found albumin in the urine.

**Summary** — Alteration in the alkalinity of the blood bathing the kidney cells probably is a factor in the production of many occasional proteinurias and has been used to explain orthostatic (including lordotic) proteinuria and the proteinurias following severe exercise and probably helps explain the decreased elimination following meals (alkaline tide). Blood flow (oxygen supply?) is probably also a factor *per se* the proteinuria decreasing during mild exercise and increasing when the blood flow is reduced as in marked stasis such as probably occurs in lordosis. This factor of blood flow suggests a close relationship between these proteinurias and the proteinuria of nephritis in which decreased blood flow may play a predominant rôle. It may also offer a partial explanation of the albuminurias in highly nervous young people where vascular instability may produce localized anoxemia. The unsettled questions are how far are these changes in kidney permeability reversible, and is there a gradation from the reversible to the chronic stages?

Senator<sup>21,22</sup> stood out among the early workers for the concept that all proteinurias have renal injury as a basis. More recently <sup>23</sup> from this point of view Thorp and <sup>24</sup> proof rests with those who <sup>25</sup> than renal injury and quote

other investigators who tend to this point of view. They divide their cases into (1) Orthostatic albuminuria, (2) albuminuria with orthostatic response, (3) latent and (4) chronic glomerulonephritis. Seventeen out of 143 cases in (1) and (2) probably dated from acute nephritis. Four cases out of 100 in the first group showed definite signs of nephritis or progressed to it. They suggest the following explanation. In accordance with previous findings (i. e. White, Rosen, Fischer and Wood<sup>6</sup>) water and such substances as urea are excreted more easily in the recumbent position. In mild renal injury albumin may not be excreted in this position whereas as soon as the upright position is assumed the kidney is not able to adjust itself and loss of albumin results. In support of this view they show that in chronic glomerulonephritis the element of orthostatic response disappears as the disease pro-

gresses. Therefore, they conclude that orthostatic albuminuria is probably in the range of mild pathological physiology.

In accordance with this point of view, lordotic proteinuria (proteinuria which appears when the subject is in the lordotic position and disappears when he resumes any other posture) might be looked upon as an even milder injury since the kidney is able to adjust itself to the upright position and requires an additional strain to induce the proteinuria. Very little work has been done with rigidly selected cases of the purely lordotic type upon which a conclusion on this point may be reached. The authors have, therefore, undertaken the following study:

### STATISTICAL STUDIES OF LORDOTIC PROTEINURIA

For comparison there are included studies of two other groups, normal individuals and individuals with constant proteinuria, classed as follows: (1) Normal individuals. (2) individuals with mild lordotic proteinuria. (3) individuals with severe lordotic proteinuria. (4) individuals with constant proteinuria. The dividing line between Groups 2 and 3 was often decided upon with some difficulty, but all cases in which urinary protein was present in sufficient amounts to be estimated quantitatively were placed in Group 3 although some slight discrepancies may have occurred on account of differences in the degrees of diuresis. Thirteen to 21 individuals were included in each group. All were between eighteen and twenty-four years of age. The control subjects in

through the courtesy of Drs Diehl and Radl. Only a few were underweight or of the so-called lordotic build. No attempt was made to correlate these two factors with the phenomenon being investigated since previous studies of this relationship seemed adequate. (See Chapter XVIII by Diehl and McKinley.) The control subjects in Group 4 comprised a miscellaneous group of ambulatory patients in the University of Minnesota Hospital and University Health Service all of whom had been diagnosed as having chronic nephritis. Most of them were in an early stage of nephritis. Two were in advanced stages.

Rehberg's creatinine-clearance test of glomerular filtration<sup>19</sup> was employed in the functional studies and was conducted as follows. The subject was given 3 gm. of creatinine by mouth and was kept in a recumbent position for one hour. Following this the test was carried out with the individual in the four following positions: (a) Recumbent kyphotic (thirty minutes). (b) standing kyphotic (twenty minutes). (c) standing lordotic (twenty minutes). (d)



standing kyphotic (twenty minutes). For statistical comparison with (c) the values of (b) and (d) were averaged (e).

Blood samples were taken at the beginning of Period 1 and at the close of each subsequent period. Urine was collected quantitatively at the end of each. From the concentrations of creatinine in these samples and the urinary volumes the minute glomerular filtrations (creatinine clearances) were figured by Rehberg's method. Protein when present in sufficient amounts was estimated by precipitating with trichloroacetic acid and subsequent ashing by Tolin's micro-Kjeldahl method.

TABLE 61. RESULTS OF REHBERG'S TEST OF GLOMERULAR FILTRATION ON 7 INDIVIDUALS INCLUDING NORMAL SUBJECTS (1) SUBJECTS WITH MILD AND HEAVY LORDOTIC PROTEINURIA (2 AND 3) AND SUBJECTS WITH CONSTANT PROTEINURIA (4). THE VALUES FOR THE MEANS AND THE STANDARD DEVIATIONS TOGETHER WITH THEIR RESPECTIVE PROBABLE ERRORS ARE GIVEN FOR TESTS IN RECUMBENT (a) KYPHOTIC (b AND d) AND LORDOTIC POSITIONS (c). IN COLUMN e ARE GIVEN THE SIMILAR STATISTICAL COMPUTATIONS FROM THE AVERAGES OF THE TWO FILTRATION VALUES OBTAINED IN THE STANDING KYPHOTIC POSITION.

Group	No. of subjects	Glomerular filtration cc per minute				
		a	b	c	d	e
		Recumbent 30 minutes	Standing kyphosis 20 minutes	Standing lordosis 20 minutes	Standing kyphosis 0 minutes	Standing kyphosis average
Mean + P.E.						
1	20	170.8 ± 4.3	171.4 ± 4.7	166.8 ± 4.7	168.5 ± 3.8	169.8 ± 5.0
2	21	153.5 ± 4.6	159.1 ± 5.9	157.8 ± 6.9	154.7 ± 8.7	153.0 ± 5.4
3	16	155.5 ± 7.0	159.0 ± 7.7	101.9 ± 8.7	148.5 ± 8.3	157.4 ± 6.6
4	13	137.5 ± 11.6	131.0 ± 9.6	93.5 ± 10.2	115.7 ± 11.1	120.5 ± 8.6
Standard Deviation = P.E. × 0.67						
1	0	27.6 ± 0.9	26.7 ± 2.9	30.3 ± 3.3	24.7 ± 0.7	21.7 ± 2.4
2	21	31.9 ± 3.5	37.8 ± 4.1	46.0 ± 5.9	36.0 ± 6.1	35.6 ± 3.8
3	18	41.7 ± 5.0	42.7 ± 5.1	51.4 ± 6.1	45.7 ± 5.6	39.3 ± 4.7
4	13	59.4 ± 8.2	47.1 ± 6.8	5.1 ± 7.2	44.7 ± 7.8	44.5 ± 6.1

**Glomerular Filtration**—Results of the functional studies are embodied in Table 61. The mean creatinine clearance in the group of individuals without proteinuria was 170.8 ± 4.3 cc per minute with a range of 121 to 208 cc per minute. Between the mean filtrations of this group and of that with mild lordotic proteinuria there was a difference of 12.3 cc per minute. This difference is not of statistical significance the ratio of the difference between the two means to its probable error being 1.9. The same general statement may be applied to a comparison of the filtrations of Groups 1 and 3 in which the lordotic proteinuria was quantitatively

greater. The corresponding ratio is also 1.9. The mean glomerular filtration of Group 4 was 137.5 cc. per minute. Here, because of the high probable error consequent upon the heterogeneous grouping, the ratio of the difference between the means of Groups 1 and 3 to its probable error is scarcely of statistical significance, being 2.7.

In no case is there a significant difference between the creatinine clearances in the recumbent and in the standing kyphotic positions. In all groups except Group 4 the value was almost the same during the two periods in this latter posture. This finding is in apparent contradiction to that of Rehberg<sup>20</sup> that glomerular filtration is lower in the upright position. It may be noted, however, that his experiments were made following periods of activity, whereas these tests had been preceded by ninety-minute periods of rest in bed.

The average values of *b* and *d* are given in column 8 (Table 61). Between the means of the filtrations in the kyphotic and in the lordotic positions (columns *e* and *c*) there is no statistically significant difference in Groups 1, 2 and 4. In Group 3 the ratio of the difference between the means to its probable error rises to 4.7 and therefore indicates that a fall in clearance in individuals with heavy lordotic proteinuria is a fundamental characteristic of the phenomenon. In 3 individuals of the group, however, the decrease was negligible, whereas in 1 case the clearance fell from 236 cc. to 44 cc. per minute. There was no such extreme fall among the normal individuals; here the greatest drop was from 238 cc. to 134 cc. per minute. In Group 4 the largest drop was from 64 to 9. Among the normal subjects the lowest rate of filtration during lordosis was 111, a value at approximately the low limit of normal. Among the individuals of Group 3 the range was from 36 to 208, demonstrating that while some of these individuals have normal filtration rates even during lordosis, others while in this attitude are characterized by rates comparable to subjects with advanced nephritis.

The majority of other workers have not reported any marked differences in functional tests between individuals with and those without lordotic proteinuria. An exception may be made in the case of Hempelmann<sup>7</sup> who reports a decrease in the phthalein output in orthostatic albuminuria. He used children of a marked lordotic build, all having heavy proteinuria, and compared them with 2 normal children. In all his observed cases there was a decreased output of phthalein in the lordotic position as contrasted with an unchanged output in normal children. The smaller number of his normal subjects, together with the extreme lordotic type of his experimental cases, does not allow any conclusions to be drawn as to gradations from normal to postural proteinuria and from postural to the mild constant type.

That individuals who have proteinuria in the lordotic position

give a more varied test than the control (Group 1) is shown by the relatively higher standard deviations as indicated in Table 61. This applied to all postures which the subjects assumed. The variability of the control individuals is not significantly increased by change of posture nor is that of those with constant proteinuria whereas in both experimental Groups 2 and 3 the standard deviations increase in the lordotic positions though not sufficiently to attain statistical significance.

**Protein Output—Posture**—Attempts to correlate fall in creatinine clearance upon assumption of the lordotic position with quantity of protein excreted by the individuals in Group 3 demonstrated that there is no positive correlation between the two phenomena. The fall in clearance varied from 9 to 180 cc per minute or from 7 to 83 per cent. The excretion of protein varied from 6 to 231 mg during the twenty minutes of lordosis. The coefficient of correlation between these two sets of data is +0.3 which is without significance in a group of 18. No correlation could be demonstrated between the amount of protein excreted and volume of glomerular filtrate either in the resting or in the lordotic position. A possible explanation for this lack of correlation is discussed later.

In Group 4 the output of protein was for the most part constant regardless of posture. In 2 individual cases however a marked increase occurred. In 1 subject the protein output rose from 30

per minute) in the second it decreased from 133 to 11 cc per minute. In general then in true nephritis the output of protein is constant regardless of posture in an occasional case lordotic proteinuria may be superimposed and may or may not be accompanied by fall of filtration through the kidney.

Medes and	t in
individuals	47
cc per minute	ute

The range was from 29.4 to 100.3 cc per minute. These values are in approximate agreement with those of the subjects of this study having mild lordotic proteinuria (see Table 61, Group 2) and differ from those with heavy proteinuria principally in their smaller probable error of the mean and standard deviation. Medes and Berglund found a statistically significant difference between the means of this group of mild proteinurics and their normal subjects whose filtrations averaged  $172.9 \pm 2.9$  cc per minute. The lower probable error in their control group was due to the larger number comprising it and indicates that with sufficiently large groups the differences between the filtration of the control subjects of this

study and of those with lardotic proteinuria might have been of statistical significance.

**Alkalinization and Acidification of the Urine**—Attempts were made to find other factors that might influence the amount of protein excreted while the subject stood in the lardotic position. Exercise and protein intake produced no effect. The effect of alkalinization of the urine noted by Post and Thomas<sup>19</sup> was confirmed. These authors found in a series of subjects with orthostatic albuminuria that protein failed to appear when the urine was alkalinized whereas proteinuria could not be inhibited by this

former instance the output of protein was increased a much greater extent upon acidification and reduced to zero upon alkalinization. In the latter case the output could not be reduced below 31 mg per ten minute period.

TABLE 62.—EFFECT OF ALKALINITY AND ACIDITY OF THE URINE ON PROTEIN OUTPUT DURING LARDOTIS IN (A) LARDOTIC PROTEINURIA AND (B) CHRONIC NEPHRITIS. THE PROTEIN OUTPUT WAS ESTIMATED PER TEN MINUTE PERIOD.

A Lardotic proteinuria				B Chronic nephritis			
Day of exper.	Feeding	pH of urine	Protein mg.	Day of exper.	Feeding	pH of urine	Protein mg.
1		6.7		1		6.7	15.0
2		6.5			1.5 gm. NaHCO <sub>3</sub>	6.0	13.7
3	3 gm. KH <sub>2</sub> PO <sub>4</sub>	5.2	1.6		1.5 gm. NaHCO <sub>3</sub>	5.7	3.1
4	3 gm. NaHCO <sub>3</sub>	5.4	9.4		3.0 gm. NaHCO <sub>3</sub>	5.5	5.1
	3 gm. NaHCO <sub>3</sub>	7.6	3.6		3.0 gm. KH <sub>2</sub> PO <sub>4</sub>	5.4	27.8
5	3 gm. NaHCO <sub>3</sub>	7.6	2.6	7	1.5 gm. NaHCO <sub>3</sub>	6.4	12.0
7	1 gm. NaHCO <sub>3</sub>	7.7			3.0 gm. NaHCO <sub>3</sub>	7.0	3.5
	3 gm. KH <sub>2</sub> PO <sub>4</sub>	7.0	3.2		3.0 gm. NaHCO <sub>3</sub>	7.1	3.2
8	3 gm. KH <sub>2</sub> PO <sub>4</sub>	5.2	15.8		3.0 gm. NaHCO <sub>3</sub>	7.1	3.5
9	3 gm. NaHCO <sub>3</sub>	5.0	47.0		3.0 gm. KH <sub>2</sub> PO <sub>4</sub>	5.5	15.0
10	3 gm. NaHCO <sub>3</sub>	6.3	17.4				
11	3 gm. NaHCO <sub>3</sub>	6.5	9.4				
12	3 gm. NaHCO <sub>3</sub>	6.5					

Change of reaction of the urine with consequent alteration in the amount of protein excreted did not affect the value of the minute filtration in any one individual. In one subject for instance, when the urine was alkalinized the glomerular filtration while he was

tions in protein output probably explains the low correlation between filtration and loss of protein in Group 3. It also opens the question of the validity of any classification of these individuals on the basis

of amount of protein excreted during lordosis. But in view of the fact that we found at least *one fundamental difference* between Groups 2 and 3 namely that in Group 3 rate of filtration was markedly affected by change of posture whereas in the group of mild proteinurias (Group 2) no such relationship could be demonstrated we must conclude that even though individuals vary widely on the average a marked fall in glomerular filtration may be expected to be associated with a high protein output during lordosis.

**Summary and Conclusions** The rates of glomerular filtration of 78 individuals between the ages of eighteen and twenty four years were determined by Rehberg's method.

The first group consisting of 20 normal individuals was found to have a mean rate of filtration of  $170.8 \pm 4.3$  cc per minute while in the recumbent position. The rate was not significantly changed upon their standing either in a kyphotic or in a lordotic position.

The second group consisted of 21 individuals whose urines were free of protein except for traces when they assumed a position of extreme lordosis. Their mean rate of filtration (recumbent position) was  $158.5 \pm 4.8$  cc per minute. Statistically considered the difference between the rate in the two positions was significant but was not significant in the whole group when tested for change of posture.

The third group consisted of 18 subjects who differed from those of Group 2 only in their heavier proteinuria when in the lordotic position. Their mean rate of glomerular filtration was approximately the same as that of the previous group  $155.5 \pm 7.0$  cc per minute. In contrast to the previous cases their mean rate of filtration was affected by posture falling to  $101.1 \pm 8.7$  cc per minute when they stood in a lordotic position.

The fourth group consisted of ambulatory patients in various stages of chronic glomerulonephritis. Their mean rate of glomerular filtration was  $137.5 \pm 11.6$  per minute. It fell to  $98.5 \pm 10.2$  cc per minute upon their assuming a lordotic posture but the high probable error due to the small number of subjects and the wide variations in their individual filtration rates made this difference of low statistical significance.

The amount of protein excreted by subjects in Group 3 showed only a slight positive correlation with decrease in rate of glomerular filtration when these individuals assumed a lordotic posture. This low correlation might possibly be explained by the fact that the amount of protein excreted varied with the reaction of the urine the proteinuria disappearing upon extreme alkalinization and reappearing upon acidification.

These quantitative changes were not characteristic of individuals

with chronic nephritis. In this group the amount of protein excreted varied somewhat with reaction but to a less extent. In individuals with mild chronic nephritis the variability was greater than in those in advanced stages.

In general individuals with lordotic proteinuria show some transitional characteristics between normal subjects and those with chronic nephritis in the following respects:

(a) Their mean rate of glomerular filtration is somewhat lower than that of normal individuals.

(b) Their filtration rates when they stand in the lordotic position vary from well within the normal range (over 100 cc. per minute) to a rate characteristic of severe nephritis.

(c) Their variability, as shown by the standard deviations of their filtration rates, increases from normal subjects through individuals subject to lordotic proteinuria to patients with chronic nephritis. In normal individuals this variability was not increased by change of posture. In the group with mild lordotic proteinuria the variability approached and in the group with severe lordotic proteinuria it equaled that of the patients with severe nephritis.

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of amount of protein excreted during lordosis. But in view of the fact that we found at least one fundamental difference between Groups 2 and 3 namely that in Group 3 rate of filtration was markedly affected by change of posture whereas in the group of mild proteinurias (Group 2) no such relationship could be demonstrated we must conclude that even though individuals vary

76 individuals between the ages of eighteen and twenty four years

was found

per minute

while in the recumbent position. The rate was not significantly changed upon their standing either in a kyphotic or in a lordotic position.

The second group consisted of 21 individuals whose urines were free of protein except for traces when they assumed a position of extreme lordosis. Their mean rate of filtration (recumbent position) was  $158.5 \pm 4.8$  cc per minute. Statistically considered, the differ-

change of posture

The third group consisted of 18 subjects who differed from those of Group 2 only in their heavier proteinuria when in the lordotic position. Their mean rate of glomerular filtration was approximately the same as that of the previous group  $155.5 \pm 7.0$  cc per minute. In contrast to the previous cases their mean rate of filtration was affected by posture falling to  $101.9 \pm 8.7$  cc per minute when they stood in a lordotic position.

The fourth group consisted of ambulatory patients in various stages of chronic glomerulonephritis. Their mean rate of glomerular filtration was  $137.5 \pm 11.6$  per minute. It fell to  $98.5 \pm 10.2$  cc per minute upon their assuming a lordotic posture but the high probable error due to the small number of subjects and the wide variations in their individual filtration rates made this difference of low statistical significance.

The amount of protein excreted by subjects in Group 3 showed only a slight positive correlation with decrease in rate of glomerular filtration when these individuals assumed a lordotic posture. This low correlation might possibly be explained by the fact that the amount of protein excreted varied with the reaction of the urine the proteinuria disappearing upon extreme alkalinization and reappearing upon acidification.

The quantitative changes were not characteristic of individuals





of amount of protein excreted during lordosis. But in view of the fact that we found at least one fundamental difference between Groups 2 and 3 namely that in Group 3 rate of filtration was markedly affected by change of posture whereas in the group of mild proteinurias (Group 2) no such relationship could be demonstrated we must conclude that even though individuals vary

78 individuals between the ages of eighteen and twenty four years were determined by Rehberg's method

The first group consisting of 20 normal individuals was found to have a mean rate of filtration of  $170.8 \pm 4.3$  cc per minute while in the recumbent position. The rate was not significantly changed upon their standing either in a kyphotic or in a lordotic position.

The second group consisted of 21 individuals whose urines were free of protein except for traces when they assumed a position of extreme lordosis. Their mean rate of filtration (recumbent position) was  $158.5 \pm 4.8$  cc per minute. Statistically considered the difference between the rates of these two groups was found to be scarcely significant but would probably have been significant had a larger group been tested. Their mean rate of filtration was unaffected by change of posture.

The third group consisted of 18 subjects who differed from those of Group 2 only in their heavier proteinuria when in the lordotic position. Their mean rate of glomerular filtration was approximately the same as that of the previous group  $155.5 \pm 7.0$  cc per minute. In contrast to the previous cases their mean rate of filtration was affected by posture falling to  $101.9 \pm 8.7$  cc per minute when they stood in a lordotic position.

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## CHAPTER XXX.

### PROTEINURIA AND PLASMA PROTEINS \*

By HILDING BERGLUND, M D, WALTER DE M SCRIVER, M D,

AND

GRACE MEDES, PH D

It was well known<sup>45</sup> that certain urines contained a substance which coagulated "like diluted serum of the blood" when a tablespoonful of urine was heated over the candle flame. Blackall<sup>46</sup> in 1813, brought out the fact that this was particularly the case in dropsies which occurred after scarlatina and likewise after treatment of lues venerea with mercury. That hematuria occurs in some patients, when the body swells after scarlatina, had been observed still earlier by von Rosenstein,<sup>47</sup> a Swedish pediatrician. The signifi-

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kidneys" and about Blackall's conclusion on heat-coagulable urine "Whether the blood is presented for secretion in a vitiated state or the urinary organs themselves perform their office imperfectly is at present not well ascertained. Through the work of Bright

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bring the question no further than to point out the presence of a marked dilution of the blood serum in some of his patients.

The development of protein chemistry was the condition for further progress. Though the separation of the chief blood proteins by precipitation with different salts was accomplished about

\* From the Biochemical Laboratory of Harvard Medical School, the Medical Service of the Peter Bent Brigham Hospital, Boston, and the Department of Medicine and the Medical Service of the University Hospital, University of Minnesota, Minneapolis, Minn. Partially aided by a grant from the Medical Research Fund of the University of Minnesota. Dr. Scriver as a National Research Council fellow was a collaborator in the work during the Boston period. Dr. Medes during the Minnesota period.

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## CHAPTER XXX.

### PROTEINURIA AND PLASMA PROTEINS \*

By HILDING BERGLUND, M D WALTER DE M SCRIVER, M D ,

AND

GRACE MEDEN PH D

It was well known<sup>16</sup> that certain urines contained a substance which coagulated like diluted serum of the blood when a tablespoonful of urine was heated over the candle flame Blackall,<sup>2</sup> in 1813, brought out the fact that this was particularly the case in dropsies which occurred after scarlatina and likewise after treatment of lues venerea with mercury That hematuria occurs in some patients, "when the body swells after scarlatina," had been observed still earlier by von Rosenstein<sup>15</sup> a Swedish pediatrician The signifi-

or the urinary organs themselves perform their office imperfectly at present not well ascertained Through the work of Bright the theory was abandoned which attributed the cause of albuminuria to the condition of the blood (hematogenous albuminuria), and the theory was introduced according to which the kidney constitutes the determining factor (nephrogenous albuminuria) Bright did not lose sight of the problem of the blood in nephritis but could bring the question no further than to point out the presence of a marked dilution of the blood serum in some of his patients

The development of protein chemistry was the condition for further progress Though the separation of the chief blood proteins by precipitation with different salts was accomplished about

the middle of the last century, it was the "salting-out" methods of Hammarsten<sup>35</sup> and Hofmeister<sup>41</sup> that led to a systematic attack upon the urinary proteins. Hofmeister studied the occurrence of lower proteins, albumoses and peptones in human urine. Earlier, in 1866, Lehmann<sup>46</sup> of Copenhagen, had tried by dilution and saturation with carbon dioxide to demonstrate the presence of small amounts of globulin in every albuminous urine. Senator,<sup>47</sup> in somewhat voluminous writings, inquired into the relationship between serum albumin and globulin in urines, expecting to find cases where globulin alone was excreted—the globulin according to Kuhne being more diffusible than the albumin. Through the work of Hoffmann<sup>48</sup> it seemed established that the ratio between serum albumin and globulin in the urine from nephritic patients is rather variable—that the albumin prevails sometimes to the extent of giving ratios as high as 10 to 1. Hoffmann pointed out the difference between this distribution and the distribution in normal blood serum and in transudates like ascites fluid.<sup>49</sup> In so doing, Hoffmann was unaware of the abnormal ratios in opposite direction which commonly exist in the blood of these patients making the contrast more marked. From 22 nephritic cases Hoffmann concluded that the albumin to globulin quotient was independent of the histological type of the kidney lesion but believed himself

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determining by weighing the globulin precipitate

Among later contributions the careful work of Csátsáry<sup>17, 18</sup> shall be mentioned carried out with Hofmeister's<sup>41</sup> method. The albumin to globulin quotients found by Csátsáry correspond well with the ones reported by Hoffm.

Csátsáry did not find any urine con-

taining only globulin

any globulin was found

globulin content with a quotient sometimes lower than unity. Other types of nephritis gave quotients varying between a little more than unity and as much as 8. Intercurrent fevers increased the relative amount of globulin excreted. Csátsáry, like Hoffmann, considered a diminution of the globulin a favorable sign.

There exists a fair amount of work from the eighties and nineties with the methods as a whole are confusing. The original methods of tedious. Thus simplified or lost. Great errors may have entered through inaccurate adjustment of the reaction of the system in the salting out process. The importance of a neutral or amphoteric reaction had been found and emphasized by Hammarsten and by Hofmeister. There is reason to suspect

that in the hands of some workers overneutralizations occurred and made the globulin disappear and there is no doubt that the large amounts of "globulin" reported by Bord<sup>10</sup> for instance were due to acidification with acetic acid during the fractionation. A similar error entered into the work of Felle<sup>11</sup>.

The question as to the occurrence of fibrinogen or fibrin in albuminous urine now presents itself. Limiting our inquiry to nephritic conditions we know spontaneous coagulation of urine to be a rare finding in nephritis caused by the use of cantharidin plaster.<sup>12</sup> According to Senator who seems first to have observed this condition serum albumin and globulin are present besides fibrin.

The question as to the amount of protein lost with the urine in acute and chronic kidney diseases and particularly the factors influencing the loss seems a simpler problem than the albumin quantitative one. The problem has hardly been tackled in a white or red meat and the effect of a straight milk diet. But whether 1 liter of milk gives less albuminuria than 3 liters the literature does not reveal.<sup>13</sup>

So far we have dealt with protein in urines secreted by diseased kidneys. As a transition to instances where protein passes through normal kidneys we meet with paroxysmal hemoglobinuria described by Dressier<sup>14</sup> about the middle of the last century. The speed of elimination and the degree of concentration of hemoglobin by the kidneys are great (hemo) and experimental observations show that albuminuria always accompanies and outlasts hemoglobinuria. Permanent kidney injury does not seem to develop even after years of repeated attacks.<sup>15</sup> Interest has long been given to the excretion of the protein which was described by Bence-Jones<sup>16</sup> in 1847 and which carries his name. This is discussed by one of us in Chapter III.

Spontaneous crystallization of protein in urine is a rare phenomenon and does not always signify Bence-Jones proteinuria. This is exemplified by a unique condition extensively and convincingly studied by Piton.<sup>17</sup> In this case with histologically normal kidneys and with no clinical symptoms of nephritis over a period of years enormous quantities were excreted of a protein which crystallized spontaneously from the urine in crystals like eggs of albumen. Piton determined the protein as a globulin. No signs of malignancy were found at the autopsy. Another interesting but obscure instance of globulinuria has been described by Britz<sup>18</sup> and

The type of proteinuria just referred to the hemoglobinuria and the Bence-Jones proteinuria might well be labeled hematogenous. Their discovery in the middle of the nineteenth century

\* Castors to be sure observed unusual crystals in urine in a case of a nephritic large amounts of white blood cells for two days

aroused interest in the experimental production of similar conditions. Hence much work was reported on the occurrence of egg albumen in the urine after the taking of raw egg white by mouth and after parenteral administration. The general criticism of the work with foreign proteins should be directed toward the methods used in ascertaining what kind of protein appeared in the urine. Efforts to correlate the experimental facts under a general viewpoint have not been wanting. The biological view held by Abderhalden accrediting the kidney with *distinguishing and eliminating* *blut fremde* proteins retained its popularity until the present dominance of the physical-chemical aspects of the blood colloids.

### RELATIONSHIP BETWEEN PROTEIN METABOLISM AND PROTEINURIA

The authors' work was begun under the impression that no conclusions could be drawn from the older literature concerning the relationship between albumin and globulin in nephritic urines. Not that the older results necessarily were incorrect but without new work taking recent development of protein chemistry into consideration an evaluation of the early results did not seem possible. Ahead of the problem of the nature of the urinary proteins an inquiry into the factors which influence or determine their elimination seemed wanted.

A suitable method for the fractionation and determination of urinary proteins had to be worked out. The method finally arrived at<sup>1</sup> for fractionation uses  $\text{Na}_2\text{SO}_4$  essentially in the concentrations used by Howe and applies the same principle for the fractionation and determination to both blood and urine. This we consider not only a convenience but a theoretical advantage.

In choosing the material for the study animal experimentation at least under the authors' hands yielded relatively little. After feeling around in different directions patients with practically unimpaired nitrogen elimination and with large amounts of urinary proteins became the first subjects for investigation. Thus most of the patients used for metabolic experiments were instances of nephrosis. The material on hand is presented independently of the chronological order in which it might have been worked up. First is presented detailed experiments on a few individuals partly the experiments may be termed metabolic. Then a description of

1. Pathological condition of the patient at the time of the fractionation of the urine.  
 degree of proteinuria  
 in the urine  
 amount of protein in the urine

Reverting to the early concepts briefly sketched above, there are presented some experiments exemplifying the *hematogenous* factor in albuminuria, followed by others where the *nephrogenous* factor might be the determining one or where it is impossible at present to decide between the two

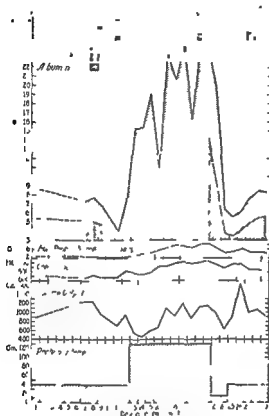


FIG 99.—Relation between level of protein intake and elimination of urinary protein  
Mr B.—Nephrosis

**The Relation Between the Level of Protein Metabolism and Proteinuria**\*—1 The results of the first experiment to elucidate this relationship are strikingly shown in Fig 99. The subject, Mr B., had been sick with heavy albuminuria and edema of

\* The authors use this opportunity greatly to acknowledge the painstaking cooperation of the dietetic services of the Peter Bent Brigham Hospital, Boston, Mass., and the University Hospital, Minneapolis, Minn.



varying intensity for more than a year. Most of this time his protein intake had been restricted. During the first period of the experiment, when the protein intake was calculated as 40 gm daily and the total calories as 2500, the plasma proteins were determined as 4.83 and 4.47 per cent, the albumin in the latter sample amounting to 0.95 per cent only. During this period the urinary (non-protein) nitrogen varied between 2.2 and 2.8 gm daily and the proteinuria

hours	four
no nitrog	was
diet calc	stein
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calories was followed by the large increase in urinary proteins, which constitutes the chief feature of this and following experiments.

The increase was prompt, the proteinuria rising from 7.55 gm protein on the last day of the low diet to 15.3 gm during the first

in the curve. During the high diet daily observations of the urinary sediment failed to reveal any signs of acute renal irritation. On the ninth day of the high diet diarrhea developed. On the eleventh day the diet was changed to rice water, tea, toast and sugar, representing about 15 gm protein and 500 Calories, which after another day was followed by the 40-gm protein diet from the foreperiod. The institution of two days of low diet was accompanied by an abrupt fall in urinary

6.39 gm only. On

urinary proteins reti

behavior of the urinary (non-protein) nitrogen during the high protein diet, rising slowly to a maximum of 8.3 gm only, clearly indicated a positive balance. Compared with the magnitude of this balance the rise of the non-protein nitrogen level of the blood was insignificant. It rose from 25.2 to 54.5 mg per 100 cc plasma. The gain from the positive nitrogen balance is reflected in the increase of plasma proteins: the total proteins rose from 4.47 to 5.75 per cent in ten days and the albumin from 0.95 to 1.7 per cent in sixteen days. The body weight first increased from 63.8 kg on the first day of the experiment to 66 kg on the nineteenth day, whereupon it fell to 60.6 kg on the last day, the twenty-ninth. The patient was confined to bed during the whole experiment. The same holds for all subsequent experiments unless otherwise stated.

2. It was thought worth while to repeat the experiment on the same patient at a later occasion. Thus, after the summer vacation in 1925 the observations presented in Fig. 100 were made. At present we wish to consider only the first thirty days of the experi-

ment. The plan for this period was the same as in Fig. 99, with the modification that the high protein diet was continued for twenty-two days. The results confirmed the first experiment in every way. The increase in urinary proteins during the high diet took place more gradually, but the peak reached before the diet

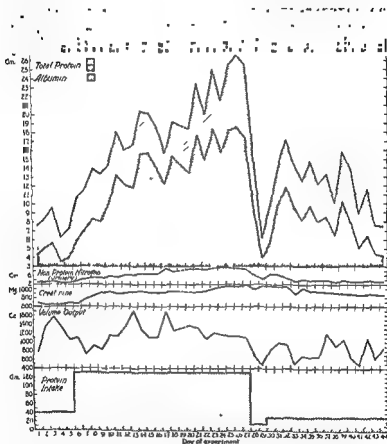


FIG. 100.—Elimination of urinary protein as influenced by (a) level of protein intake (b) fever and (c) blood transfusion. Darnumson on pages 476 and 479. Mr. Liu Nephrosis.

was altered was higher the maximum twenty-four-hour output being 26.6 gm *versus* an average of 7.5 gm during the foreperiod. The decline in protein output following the change in diet was as abrupt and far-going as in Fig. 99, the protein elimination during the twenty-eighth and twenty-ninth day (Fig. 100) being 15.22 and

6.15 gm, respectively. As in the preceding experiment a positive nitrogen balance existed the nitrogen excretion was 1.4 gm.

TABLE 63 — ALBUMIN IN PER CENT OF TOTAL URINARY PROTEIN DURING DIFFERENT LEVELS OF PROTEIN INTAKE MR. B. J. NEPHROSIS

Dietary condition	Albumin content of urinary protein		
	Mean $\pm$ P.E.	$\sigma$	
I Five days foreperiod on 40 gm protein daily	58.0 $\pm$ 0.73	2.15	
II First five days on 130 gm protein daily	61.3		
III Subsequent twelve days on same diet	75.4 $\pm$ 0.50	2.45	I Difference between mean III and mean I of high significance ratio between difference and probable error of difference = 19.7
IV Last five days on high diet	71.0		
I-IV Whole period of high diet	71.2 $\pm$ 11.9	6.63	II-IV Difference between mean II-IV and mean I significant ratio between difference and probable error of difference = 11.3
V First three days on subsequent low diet 15 to 30 gm protein daily	67.5 $\pm$ 1.40	2.94	V Difference between mean II-IV and mean V significant ratio between difference and probable error of difference = 4.93

The experiment further provides a continuous record of the relation of albumin to globulin in the urine (Table 63). During the foreperiod the albumin constituted an average of 58 per cent of the urinary protein; during the high diet this ratio gradually changed, so that during the eleventh to the twenty-second day of

continuation of the high diet the albumin was reduced more than the globulin, the albumin falling to 62.5 per cent of the total protein.

In number of grams of protein excreted this patient among all studied showed the greatest response to the experimental condition.

The positive nitrogen balance likewise was more marked than in any other patient. The experiments so far reported clearly bring out the independence of the proteinuria of the level of the protein metabolism if measured by the urinary (non protein) nitrogen, but its dependence on the level of the protein intake.

3 The following 5 experiments were carried out in order fully to establish the relationship between protein intake and proteinuria. The experiment presented in Fig 101 pertains to a young girl, Miss

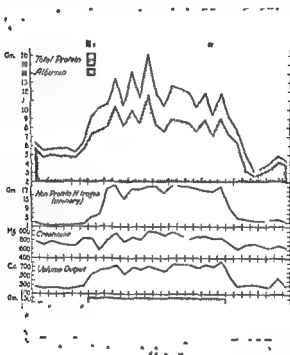


FIG. 101. Relation between protein metabolism and protein elimination. Miss Hx Nephrosis

Hx aged sixteen years, with a typical nephrosis. The circumstances in this experiment in one respect differ from the previous

nitrogen of the plasma from 23 to 56 mg during the high diet must

not be  
caloric  
and 20

daily The weight at the beginning of the experiment was 54.5 kg  
at its end 50 kg the drop was gradual

The urinary protein response to the changed protein intake was

of the high diet The decline of the proteinuria at the end of the  
high diet was prompt The total increase in proteinuria was smaller  
than in the first patient in spite of essentially identical conditions  
in diet and protein output during the foreperiod

The ratio between albumin and globulin differs from the ratio in  
the first patient During the foreperiod the albumin constituted  
 $87.1 \pm 0.52$  per cent of the urinary protein during the high diet  
the ratio fell to  $74 \pm 0.49$  per cent a significant difference and  
rose during the afterperiod to  $83.6 \pm 0.73$  per cent revealing an  
opposite behavior to what was observed in the second experiment \*  
The effect of the high diet upon the plasma proteins was slight and  
also different from the previous experiment the total protein increas-  
ing from 6.16 to 6.35 per cent only and the albumin decreasing  
from 1.15 to 0.73 per cent We shall return to these opposite types  
of response and attempt partly to correlate them with the different  
nitrogen balances in the first and second patient

4 The experiment presented in Fig. 102 was carried out on a  
patient with typical nephrosis Mr. Edwin T. r. aged twenty five  
years At present will be considered the first thirty days of the  
experiment only The patient was in the comparatively early  
stage of the disease

worse instead of better

by the twelfth day on

protein diet From

given calcium chlor

gastrointestinal upset the high diet was used

in Fig. 102 From the twentieth to the twenty third day the  
caloric intake was about 500 daily otherwise 2500 The nitrogen  
balance during the high diet was definitely positive

The urinary protein during the foreperiod was rather variable in

as follows  
= difference  
the second

amount increased output in response to the high intake followed by diminished output when the protein intake was reduced is shown in Fig 10<sup>7</sup> just as in previous experiments. The ratio between urinary albumin and globulin in this patient deserves attention. While the patient was in the Deaconess Hospital Boston Mass we had opportunity through the courtesy of Dr Howard I Root to examine a sample of his urine. It contained a large amount of

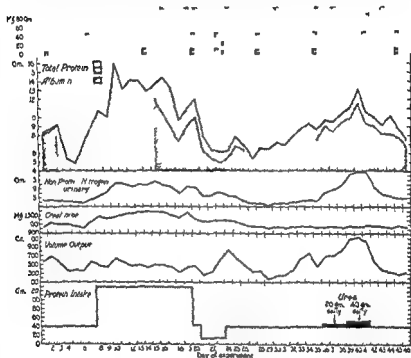


FIG 10<sup>7</sup> Fluctuation of urinary protein as influenced by a level of protein intake and (b) excretion of urea. Discussion on pages 44 and 45. Mr Edwin T. Nephros.

stituted 9, 37 and 100 per cent of the total proteins. The urinary proteins were again fractionated when the patient during high protein diet was taking calcium chloride the results were 88.5 and 11.5 per cent albumin. After discontinuation of the calcium chloride and shift to low diet the albumin gradually increased to

93.2 per cent. This cycle in principle corresponded to what was

contributed to the increased loss of globulin. That such was not the case may be concluded from observation on Alvin J., to be

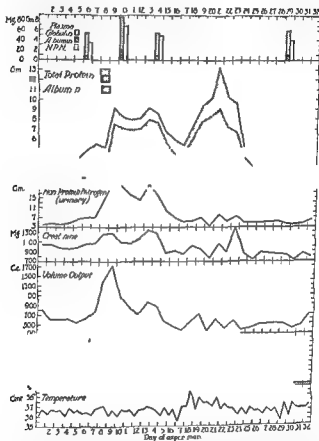


FIG 103 : Elimination of urinary protein as influenced by (a) protein metabolism and (b) fever. Discussion on pages 484 and 485. Mr. Was Nephros.

E. L. J.

average above the rate of protein loss during the foreperiod and on discontinuation of the high diet promptly started to decline. The urinary albumin during the last days of the foreperiod fell from 96 to 74 per cent of the total protein dropped during the first two days of high diet to 66 per cent then still during the high diet increased to 89 per cent. The plasma proteins showed an unusual and transitory increase early during the high diet from 5.32 to 8.75 per cent for the total proteins and from 0.75 to 2.11 per cent for the albumin. Once later a similar large increase was observed. In Mr. Wss there was a combination of high protein diet and rapid loss of edema.

The experiments described were carried out on typical instances of nephrosis: the patients were sick people with pronounced edema. The next 2 experiments are believed to be of value as contrasts to the previous ones. They were carried out on 2 patients without any other pathological signs than albuminuria: the condition in both instances having been picked up accidentally through routine urine examination. During the whole period of the experiments the renal condition showed no signs of change nor were there in either case any signs of active renal irritation. The factors entering into the experiments thus seem limited to a chronic condition of

Alvin J. s. who presented no other abnormal signs than a reversed proportion of albumin and globulin in the plasma and albuminuria without pathological sediment. Before the high protein diet the total plasma proteins were: fibrinogen 0.4 gm, euglobulin 1.1 gm, logglobulin 1.1 gm, or total albumin 2.2 gm, and total foreperiod on low protein gm = 0.06, on change to high protein diet it increased after one day's lag to 7.12 gm, the elevation outlasting the high diet by two days whereupon there was an abrupt return to the level of the foreperiod. The mean output for the six days with high proteinuria was 6.46 gm  $\pm$  0.18, the output for the seven days following the abrupt drop (fifteenth



eleventh and eighteenth day of the experiment precipitation curves 1 2 and 3 respectively in Fig 105 The albumin on the low diet constituted 96 per cent of the urinary protein fell during the high diet to 50 per cent and on return to low diet likewise returned

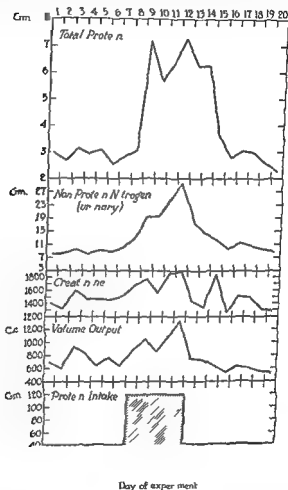


FIG 104 —Relation between protein excretion and level of protein intake Mr Alv n J ■ Symptom free albuminuria later recognized as chronic Nephritis

to 97 per cent This behavior is identical with what was found to be the case in Experiments 3 to ■ In the present experiment the observations are more detailed and there is in the experiment nothing to suggest anything but a pure physical mechanism nothing indicating aggravation of the renal damage

7 The last experiment in this group was carried out on Mr Laurence R. aged thirty-six years in whom symptomless albuminuria was discovered while the patient was being treated for a fresh syphilis at the Boston Dispensary. During the long metabol-

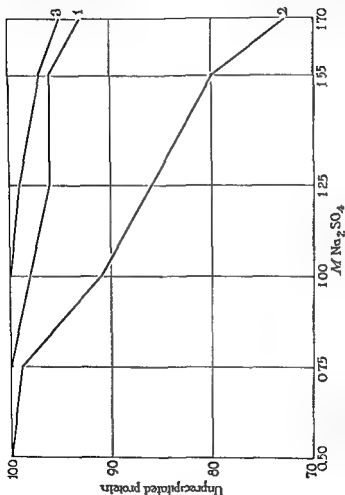


FIG. 103.—Precipitation curves for urinary protein from experiment of Fig. 104. Curve 1 during period of low protein diet; curve 2 during subsequent low protein diet; curve 3 during subsequent high protein diet.

ism experiment different short experiments reported below were run. There have been condensed in Table 64 the parts of the high and low protein experiment which with certainty were uninfluenced by the other experiments. Table 64 shows the same response as the

preceding experiments an increased protein output on high protein diet and a lesser protein loss upon return to low protein intake. The differences between the mean output during the high protein period,  $6.93 \text{ gm} \pm 0.25$  and during the foreperiod and afterperiod  $4.23 \text{ gm} \pm 0.12$  and  $2.88 \text{ gm} \pm 0.14$ , respectively, are statistically significant. The ratios between the respective differences and their corresponding probable errors are 9.7 and 14.1, respectively.

TABLE 64—SHOWING INCREASED PROTEIN LOSS IN THE URINE ON HIGH PROTEIN DIET

Subject *Mr. Laurence R. I.* Aged *Thirty six Years* Diagnosis *Syphilitic Nephrosis*

Date	May July 1925	Condition	Plasma		Urinary protein	
			Total protein per 100 cc gm	Albumin per cent of total protein	Mean 24 hour output gm	Standard deviation ( $\sigma$ )
I	Foreperiod (11 days)	Diet 40 gm protein No meat 3500 Cal	4.96	35.7	$4.23 \pm 0.12$	0.56
II	High protein diet (9 days)	130 gm protein High meat 2500 Cal	$6.12 \pm 0.90$	$33.3 \pm 30.0$	$6.93 \pm 0.25$	1.05
III	After period (10 days)	Same as I	5.05	48.5	$2.88 \pm 0.14$	0.87

The ratio between urinary albumin and total urinary protein was frequently determined and varied between 98 and 80 per cent with the mode between 92 and 88 per cent. The plasma proteins increased approximately 2 gm per 100 cc on the high diet the increase being greater in the fibrinogen globulin than in the albumin fraction.

These constitute our total number of uncomplicated experiments with high and low protein diets in chronic albuminuric conditions. That there exists a hematogenous factor in albuminuria as was held before Bright and is held today by Epstein and the investigators who follow him is brought out by these experiments. The conditions are decidedly complicated. So far we have dealt with the following factors:

the positive or relative proportion of the plasma itself

### PROTEINURIA AND MYXEDEMA

8. The authors have still another experiment with high and low protein diets on a patient in whom the condition of heavy albuminuria was complicated by myxedema or vice versa. The patient,

Mrs. A-e, aged fifty-five years, entered the hospital with myxedema, heavy albuminuria, slightly decompensated heart and some edema beyond the myxedematous condition. The renal condition corresponded well with a nephrosis, the renal function was good, the blood-pressure not elevated. The patient had not received thyroid medication prior to the hospitalization. While the patient was receiving desiccated thyroid it was noticed that the albuminuria was greatly increased. In the meanwhile the metabolic rate had returned toward normal. For the sake of the experiment just to be described the thyroid medication was discontinued and the meta-

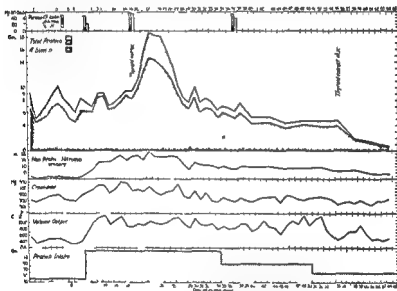


FIG. 100 — Elimination of urinary protein as influenced by thyroid administration. Mrs. A-e. Combination of heavy albuminuria and myxedema.

bolic rate was allowed to drop back to  $-40$ . The patient was then given meat-free diet containing 40 gm. protein and 2000 Calories. She was confined to bed. Fig. 100 and Table 65 reproduce the essential features of the experiment. There was during the foreperiod a positive nitrogen balance, moderate but definite. The response to the high protein diet, calculated to contain 131 gm. protein including much meat, was prompt as far as the (non-protein) nitrogen elimination went. But though this response

the difference lacking statistical significance. For the first time we met with a heavy proteinuria which did not respond to increased protein intake with markedly increased proteinuria. There was however, another sign of altered protein metabolism, the same as was observed in the first patient, Mr Bsi, who showed a positive nitrogen balance more pronounced than the patient now under discussion. This refers to the change in the proportion of albumin in the urinary proteins. The authors' first patient Mr Bsi showed a relatively low albumin content on low protein diet, which content increased significantly on high protein diet, simultaneously

TABLE 65—RELATIONSHIP BETWEEN PROTEIN INTAKE, THYROID FEEDING AND PROTEIN OUTPUT IN MYXEDEMA WITH HEAVY ALBUMINURIA  
Mrs A c Aged Fifty-five Years

Condition of experiment	Protein output Mean $\pm$ P.E.	Ratio *	Albumin per cent of total protein Mean $\pm$ P.E.	Ratio *	Nitrogen output (non protein) Mean $\pm$ P.E.	Ratio *
I Nine days (pre- ceded on 40 gm protein intake)	Gm 7.92 $\pm$ 0.38		76 $\pm$ 0.61		Gm 2.9 $\pm$ 0.12	
II Seven days on high protein diet 130 gm without thyroid medica- tion	8.34 $\pm$ 0.38	0.89	91 $\pm$ 0.65	16.42	13.3 $\pm$ 0.73	13.54
III First ten days of thyroid medica- tion and high protein diet	14.09 $\pm$ 0.87	6.29	81 $\pm$ 1.14	7.53	16.1 $\pm$ 0.45	3.17
IV Six subsequent days conditions same as in III	8.0 $\pm$ 0.37	6.43	83 $\pm$ 0.60	1.33	10.6 $\pm$ 0.49	8.38
V Twenty-two sub- sequent days on thyroid medica- tion but lower protein intake	5.26 $\pm$ 0.13	7.04				
VI Nine subsequent days without thy- roid medication	1.37 $\pm$ 0.10	23.7 <sup>a</sup>				

\* Ratio =  $\frac{\text{difference of two means}}{\text{probable error of the difference}}$

with a heavy increase in proteinuria. All subsequent patients up to the present one had shown the opposite phenomenon a high albumin content on the low diet and a greater proportion of globulin in the urine. In harmony with this phenomenon but contrary to what is most commonly observed the plasma proteins during the same period showed their greatest increase not in the fibrinogen globulin but in the

albumin fraction the total increase being from 4.93 to 5.7 gm. per 100 cc. of which the albumin constituted 19.1 and 31 per cent.

low diet never fully to return to the high values immediately before the thyroid medication. The urinary (non protein) nitrogen during the same period of high protein elimination likewise showed an increase but less marked than the protein.

Under continued thyroid medication the protein intake was reduced first to 90 gm. and sixteen days later to 60 gm. daily. During this time there was a gradual drop in the urinary proteins to between 4 and 5 gm. daily. During this time the albumin fluctuated between 80 and 89 per cent of the total protein. When after thirty-six days of thyroid medication its administration was discontinued the urinary proteins promptly fell from between 4 and

was started. Less than one month after the end of the experiment the urine became free of albumin and remained so for the subsequent four years. The thyroid medication was resumed shortly

substance to myxedematous and normal individuals (Magnus-Levy, Grafe, Boothby and collaborators). Of interest from the point of view of the present experiment is Boothby's interpretation of this phenomenon as due to a mobilization of reserve protein particularly the amount contained in the myx edema. In the case of Mrs. A-e we failed to obtain an unquestionably significant increase in the urinary (non protein) nitrogen following the administration of desiccated thyroid, but obtained a highly significant

leaking large amounts of protein escaped through the kidneys before deamination could occur. On this point one recalls Thompson's demonstration of increased plasma volume immediately following

substitution therapy in myxedema In the subject of Experiment 6, Alvin J s, desiccated thyroid was administered but failed to increase the protein elimination

### MISCELLANEOUS INFLUENCES UPON PROTEINURIA

The experiments so far presented have dealt with the hematogenous factor in proteinuria Next will briefly be described a motly variety of short experiments some elucidating the nephrogenous or renal factor, others leaving us without possibility to decide between one or the other Most of these experiments were done early during this work with the purpose of ascertaining and eliminating the factors which were most apt to interfere with the metabolic experiments The experiments deal with the effects of diuresis as studied by the dilution concentration test, of posture, of sodium chloride, of calcium chloride given to produce an acid and sodium citrate to produce an alkaline urine, of urea, of injection of arsphenamine, of blood transfusion and of fever

Cushny's review of albuminuria<sup>20</sup> brings out how scanty is the knowledge of the factors which influence its amount and composition The view first advanced by Runeberg,<sup>21</sup> a Finnish clinician and supported by Cushny, of the glomerular structure as responsible is based as much upon ion as upon histological glomerular capsule

Table 66 shows in some detail the behavior of urinary protein during a dilution-concentration test on Mr Laurence R, the subject in Experiment 7 When this test was run the patient was on low protein intake During two hours from 8 to 10 A M the specific gravity fell from 1 030 to 1 001 the diuresis increased from a rate of 16 5 to 335 cc per hour and the protein concentration fell from 710 to 31 mg per 100 cc urine In another hour's time from 10 to 11 A M the specific gravity climbed to 1 014, the diuresis fell from 335 to 43 cc per hour and the protein concentration rose from 31 to 247 mg per 100 cc urine With these extensive variations in the composition of the urine the protein output per hour remained practically as constant as the creatinine output the latter varying  $\pm 8$  per cent and the former  $+17$  and  $-10$  per cent from the output of the two hour foreperiod between 6 and 8 A M From 9 A M to 12 NOON, during which time the composition of the urine changed considerably, there was no variation either in protein or in creatinine elimination

The experiment conclusively shows the rate of protein elimination to be independent of the concentration of the urine of the rate of diuresis and of the urinary protein concentration Incidentally it demonstrates the futility of estimating, quantitatively or semi-

quantitatively the amount of albumin in a urine sample without taking into account specific gravity or diuresis

TABLE 66 DILUTION-CONCENTRATION TEST SHOWING THE ALBUMIN OUTPUT TO BE INDEPENDENT OF THE DIURESIS

Subj *et* Mr. Lawrence E. L. Age 47 Th. 175-cm. Yrs. 5 Days 6 Albuminuria in Syphilis

Time	Condition	Urine						
		Amount cc	Specific gravity	Protein per 100 cc	Protein per hour	Protein per 24 hours	Albumin per cent of total	Creatinine per hour
June 7	Low protein diet	365				2.78	84.0	
8		350	1025			4.00	94.7	
9								
6 A.M.	8 A.M. 1000 cc water by mouth on empty stomach	33	1030	710	117		84.0	50
9 A.M.		112	1006	1	19		91.0	51
10 A.M.		335	1001	31	105		85.4	46
11 A.M.		74	1007	143	100		93.6	46
1 P.M.	Dry luncheon	43	1014	4	100		87.0	45
3 P.M.		141	101	78	124		9.9	49
6 P.M.	From 6 P.M. free fluid intake	104	1020	445	161		8.6	45
7 A.M.		161	1024	67	24	2.79	84.0	44
June 10		365	1034			4.34	84.7	
11		365	1035			4.60	89.0	

For the creatinine the accepted interpretation of its constancy is a constant production of excretable creatinine as far as this experiment goes.<sup>41</sup>

discussion It is well to mean that the experiment forms a counter piece to the straight line filtration curves given by Medes and Berglund as Fig. 43 in their paper on Rehberg's test (page 217). Such is the authors' interpretation of the experiment.

Another dilution-concentration test on the same patient while on high protein diet. Table 67 is interpreted in light of the curves of creatinine.



between 8 and 9 A.M. as the first effect of the ingested water in opening up a greater number of glomerular capillaries. The same effect was noticeable in Table 66, where the urine secreted between 8 and 9 A.M. carried with it a slightly increased amount of protein. Returning to Table 67, there was a gradual drop in protein excretion from 9 A.M. during the remainder of the forenoon, just as in the curves on page 493.

TABLE 67—DILUTION-CONCENTRATION TEST SHOWING PROTEIN ELIMINATION TEMPORARILY INCREASED COINCIDENT WITH ONSET OF DIURESIS BUT INDEPENDENT OF THE HEIGHT OF THE DIURESIS

Subject Mr. Laurence R-1 Aged Thirty-six Years. Diagnosis Albuminuria in Syphilis

Time	1925	Condition	Urine					
			Amount cc	Specific gravity	Protein per 100 cc mg	Protein per hour mg	Protein per 24 hrs gm	Creatinine per hour mg
June 27		High protein diet with meat	890	1027			5.70	1390
28			760	1026			6.00	1335
29								
6-8 A.M.		8 A.M. 1000 cc water by mouth on empty stomach	56	1035	899	168		55
9 A.M.			108	1008	208	224		57
10 A.M.			335	1005	46	155		54
11 A.M.			62	1010	209	129		54
12 NOON		Dry luncheon	54	1012	205	111		55
3 P.M.			105	1001	332	134		57
6 P.M.		From 6 P.M. free fluid intake	112	1024	453	169		62
7 A.M.			410	1005	439	133	3.66	65
June 30			830	1025			6.84	1372
July 1			875	1032			9.95	1421

It is carried out on Mr. B-1. It should be recalled that the diuresis resulting from the

ingestion of 1

Mr. R-1 the

to 172 cc in

The 54-cc ur. . . .

the drinking of the water showed the maximum proteinuria, 201 mg, as versus 194 mg during the preceding and 200 mg during the fol-

lowing hour. The creatinine output was constant to the milligrams from hour to hour.

These experiments are presented as examples of the renal factor in proteinuria.

It will be noticed that in both Tables 66 and 67 the day of the water test showed a twenty-four-hour protein output significantly lower than the respective averages. The same was the situation in Mr. B. For this phenomenon no explanation can be offered. The total caloric intake during the days of the test was divided between two meals instead of three. On the strength of these observations, and since the metabolism experiments were run on patients without renal insufficiency, we have made it a rule to keep the urinary volume nearly constant by restricting the fluid intake.

TABLE 64.—SHOWING THE EFFECT OF BODILY POSITION AND ACTIVITY ON THE ELIMINATION OF URINARY PROTEINS

Subject Mr. Laurence R. I. Aged Thirty-six Years Diagnosis Albuminuria in Syphilis

Time 1915	Condition	Urine			
		Amount cc	Protein per four mc	Protein per 24 hours gm	Creat- inine per hour mg
May 19					
7 9 A M	In bed all day	29	59		50
9-11 A M		32	66		72
11 1 P M		37	74		86
1 P M					
7 A M		345	102	2 23	54
May 21					
7 9 A M	Out of bed and actively walking about from 9 to 10 30 A M	74	124		64
9 11 A M		65	236		59
11 1 P M		122	133		83
1 P M					
7 A M		285	137	3 45	49
June 10		365		4 31	1150
11		395		4 50	1130
12		340		3 36	1080
13	Out of bed walking all day	610		8 05	1220
14		350		5 84	1175
15		350		2 65	1060
16		330		1 35	1010
17		645		2 36	1071

unchanged protein output while out of bed for two days. With these experiments excepted during all our observations the patients have been confined to bed.

TABLE 69—SHOWING TEMPORARY DEPRESSION OF URINARY PROTEINS FOLLOWING ADMINISTRATION OF SODIUM CITRATE

Subject Mrs. B. Aged Forty-three Years Diagnosis Chronic Nephrosis

Time 1925	Condition	Body weight kg	Urine		
			Amount cc	Protein per 24 hrs gm	Creatinine per 24 hrs mg
June 10	Low protein diet	63.0	575	7.00	695
11			850	10.08	800
12			690	7.90	800
13			1035	8.18	850
14	Sodium citrate 20 gm sodium citrate 20 gm	63.3	660	3.00	755
15		64.0	545	6.61	705
16		63.8	880	8.69	705
17		65.0	720	7.23	706
18					

TABLE 70—SHOWING THE INFLUENCE OF ALKALI UPON PROTEIN ELIMINATION

Subject Mr. Laurence R. Aged Thirty-six Years Diagnosis Albuminuria in Syphilis

Time 1925	Condition	Body weight kg	Urine		
			Amount cc	Protein per 24 hrs gm	Creatinine per 24 hrs mg
June 3	Low protein diet	56.0	1035	3.80	1335
4			775	3.91	1040
5			465	2.91	1180
6			435	3.10	1040
7			355	3.28	1190
July 6	High protein diet	54.0	365	3.78	1105
7			845	9.89	1535
8		54.6	865	6.85	1559
9			1085	4.67	15
10			945	5.30	1497
11			825	12.40	1400
12			500	5.13	1370
		54.6	815	8.14	1595

intake was not increased

Opportunity to observe the effect of fever or of infection upon proteinuria offered itself in Mr W- (Fig 101) who on the fourth day after the discontinuation of the high protein diet developed an acute infection of the remaining lymphatic tissue of the throat. The temperature (oral) rose to  $38.5^{\circ}\text{C}$  was on the second day  $37.9^{\circ}\text{C}$  on the fourth day  $37.8^{\circ}\text{C}$  on the fifth or sixth day back to normal. Increased protein output accompanied the infection, surpassed the proteinuria of the preceding high diet and reached

13.3 gm the fourth and last day of the fever, whereupon it fell abruptly to a slightly lower level than before the high protein diet. The albumin fraction of the urine fell during the fever from 85 to 65 per cent at the height of the protein output, again to return to 80 and 85. The creatinine elimination showed a sharp peak with the return of normal temperature.

This observation lends assurance to the interpretation of the last part of Fig. 100 picturing the second experiment on Mr. B. On the thirty-first day of that experiment the patient's temperature rose to  $99.6^{\circ}\text{F}$ . there was pain in the left side of the chest with a friction rub. Simultaneously with this evidence of infection the protein elimination rose abruptly, reaching 17.3 gm on the second day; the pleural irritation subsided; the temperature was normal again the second day and remained so and the protein output started on a downward course.

After the protein output on the thirty-eighth day had come down to 10.14 gm a blood transfusion was given on the thirty-ninth day of the experiment. Citrated blood was transfused, 450 cc containing 250 cc plasma of a protein content of 7.65 per cent and a ratio of albumin to globulin of 1.35 to 1. The recipient's plasma before the transfusion contained 5.9 per cent protein with a ratio of albumin to globulin of 1 to 2.11. Immediately after the transfusion the plasma concentration was 5.63 per cent and the ratio of albumin to globulin was determined as 1 to 1.98. There was no transfusion reaction. The urinary proteins the day of the transfusion were increased to 15.9 gm and the following day to 13.85 gm whereupon the downward course of the proteinuria was resumed.

+ + + + + the increased proteinuria in fever  
enous  
other

## STUDY OF PLASMA AND URINARY PROTEIN FRACTIONS

Though the different proteins which make up the plasma have long been studied and their individuality recognized—years ago

and the albumin have been distinguished by their biological response

When on the following pages we speak of fibrinogen, euglobulin

\* It is outside the scope of this report to enter into a discussion of the chemistry of the plasma proteins. Among several valuable discussions of this topic the following are called to the reader's attention: Sørensen S. P. L. Proteins lectures given in the United States of America in 1924. The Fleischmann Laboratories 1925. Limited edition. Hynd. Lancet ii 910 1925. Hewitt. Biochem J 21 216 1927. Cayett and Gibson. J Clin Invest 10 857 1931. Widdowson. Biochem J 27 1371 1933.

pseudoglobulin I, pseudoglobulin II and albumin we do so for the sake of convenience to save the reader from the descriptive expressions the protein fraction precipitated between sodium sulphate concentrations of 0.5 and 0.75 M (fibrinogen) of 0.75 and 1 M

authors graphic presentations they retain the expression of the molarity of the precipitant instead of the conventional names. The textbooks of biochemistry inform us that the different fractions may be separated and characterized by other means than by their solubility in sulphate solutions. In the separation by the salting-out process which we have used the fact should be called attention to that in normal plasma the precipitation from 0.5 to about 1.4 or 1.45 M  $\text{Na}_2\text{SO}_4$  is continuous without any neutral zones and that it is only between approximately 1.45 and 1.55 M that no precipitation takes place. Thus it is only in the separation of the

bility described above which has not been checked as fibrinogen, for instance by determination as fibrin. The fact that normal fibrinogen values obtained by both methods check completely gives slight guarantee that the same holds for pathological material though fibrinogen concentrations at least three times normal have been determined as fibrin (Grøn<sup>24</sup>). The fibrin method on the other hand might under circumstances give too low values.

Whatever the chemical individuality of the protein fractions may be as the salting-out method now stands with the conditions under which the precipitation takes place properly worked out the method affords a means of an objective and quantitative description and characterization in regard to solubility of plasma and urinary proteins. As such the authors have used it.

The common knowledge about the functional behavior of the plasma proteins consists of a few facts for instance that the fibrinogen globulin fraction is increased in animals used for the production of specific immune bodies during pregnancy and in patients afflicted with kala-azar and leprosy and that the albumin fraction may be greatly reduced in nephrosis and nephritis. The authors have twice observed instances where the albumin was reduced to 0.25 per cent and the reader's attention may already here be called to the massive increase in the fibrinogen-euglobulin content depicted in Fig. 111 (page 535). The existence of an enormous capacity to synthesize plasma proteins must be concluded

from the necessity of large and frequent plasmapheresis in order to maintain hypoproteinemia in dogs. On shifting a dog (recovering from uranium poisoning) from low to high protein diet the authors observed a change in plasma protein concentration from 5.31 to 8.27 per cent in five days. In this particular instance the increase was about equally divided between the albumin and globulin fractions, prompting the question to what extent the change in concentration was due to dehydration or to synthesis of new proteins. This problem usually does not enter in, as exemplified in Mr. W-s (Fig. 103) in whom on change from low to high protein diet within four days the plasma proteins rose from 5.32 to 8.75 gm. per 100 cc., with the albumin fraction going from 14 to 28 per cent. In a more recent observation in a patient (Malberg) convalescing from acute nephritis with colossal edema the total proteins rose from 5.36 to 7.02 per cent and the albumin from 0.43 to 2.3 per cent or more than the total increase, indicating a complete change of pattern. Equally striking changes in opposite direction within very short time are also observed, as in a patient (E-v-l) with chronic nephrosis edema-free and in full activity on high protein diet. This patient had 6.59 per cent protein in his plasma of which 2.16 per cent was albumin. After four days on low protein diet his total

rather than the average run have been chosen in order to engage the reader's interest in the following statistical study of the plasma and urinary proteins.

TABLE 71. COMPOSITION OF NORMAL PLASMA PROTEINS

Protein	Mean $\pm$ P.E.	Standard deviation ( $\sigma$ ) $\pm$ P.E.s	Coefficient of variation
Fibrinogen	0.294 $\pm$ 0.010	0.060 $\pm$ 0.007	21.0
Euglobulin	0.681 $\pm$ 0.067	0.389 $\pm$ 0.044	57.1
Fibrinogen and euglobulin	0.974 $\pm$ 0.065	0.407 $\pm$ 0.046	41.8
Pseudoglobulin	0.939 $\pm$ 0.049	0.306 $\pm$ 0.034	32.5
"	0.691 $\pm$ 0.041	0.255 $\pm$ 0.029	37.9
"	"	$\pm$ 0.030	17.2
"	"	$\pm$ 0.040	12.9
"	"	$\pm$ 0.030	11.4
"	"	$\pm$ 0.070	8.7

Values representative of normal concentration and normal variability of plasma proteins are presented in Table 71. The material consists of determinations in 19 normal individuals, physicians and assistants around the laboratory. The mean total protein concentration was 6.66 per cent  $\pm$  0.09, the albumin was 4.07 per cent  $\pm$

0.07 and the fibrinogen globulin fraction 2.59 per cent  $\pm 0.05$ . These values are identical with the means obtained by Under, Lundsgaard and Van Slyke from eight determinations on 7 individuals.

and coefficient of variation for each group

Table 72 contains corresponding information about pathological plasma. Table 72 is based upon 44 plasmas from practically the same number of patients predominantly afflicted with renal disease, some with diseases of heart, liver, blood or bone-marrow. No patients with kala-azar, leprosy, acute pneumonia or acute yellow atrophy are found among our material.

TABLE 72. COMPOSITION OF PATHOLOGICAL PLASMA PROTEINS

Protein	Mean $\pm$ S.E.	$\sigma \pm$ S.F.	Co-efficient of variation
Fibrinogen	0.47 $\pm$ 0.03	0.400 $\pm$ 0.040	10.0
Fuglobulin	0.54 $\pm$ 0.03	1.030 $\pm$ 0.030	19.0
Fibrinogen and fuglobulin	1.01 $\pm$ 0.10	1.430 $\pm$ 0.030	20.0
Fibrinogen and fibrin	1.130 $\pm$ 0.03	0.440 $\pm$ 0.07	3.0
Fibrinogen and fibrin	1.774 $\pm$ 0.02	0.304 $\pm$ 0.025	3.5
Fibrinogen and fibrin and fibrin	1.900 $\pm$ 0.030	0.507 $\pm$ 0.077	7.0
Total globulin (including fibrinogen)	1.470 $\pm$ 0.110	1.560 $\pm$ 0.030	41.0
Albumin	2.960 $\pm$ 0.030	1.070 $\pm$ 0.030	30.0
Total protein	6.430 $\pm$ 0.120	1.100 $\pm$ 0.030	20.0

The mean total protein was 6.43 per cent  $\pm 0.12$ , which figure does not vary significantly from the normal mean, the ratio of the difference to the probable error of the difference being  $-1/3$ . The standard deviation and the coefficient of variation for the total protein are 0.12 and 20.0.



While the albumin showed diminution, the total globulin, including

larger than for the normal

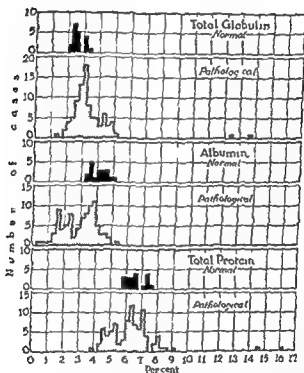


FIG. 107.—Distribution of normal and pathological plasma protein values

of the difference and the probable errors of the difference being 3.3. To

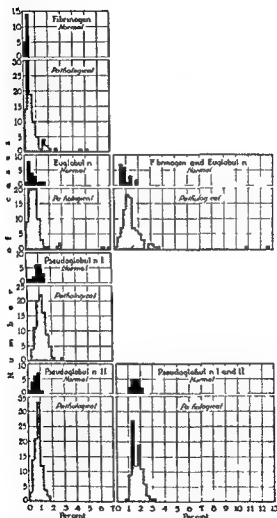
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FIG. 108.—Distribution of normal and pathological plasma protein values.

pathological albumin. For this fraction the material did not prove homogeneous showing two groups of slightly different size one approximately of normal values the other with lower values. No such cleavage is present in the other fractions from the same plasmas. The group with the lower

While the albumin showed diminution the total globulin including fibrinogen showed significant increase the mean being  $3.47$  per cent  $\pm 0.11$  as *versus* the normal  $2.59 \pm 0.05$ . The difference is significant the ratio of the difference to the probable error of the difference being  $7.3$ . The coefficient of variation for the pathological group is more than three times larger than for the normal.

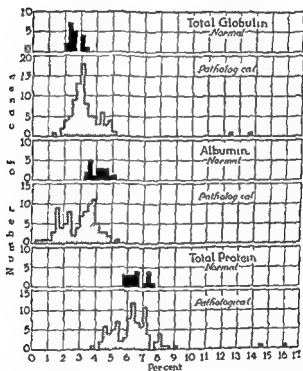


FIG. 107 — Distribution of normal and pathological plasma protein values

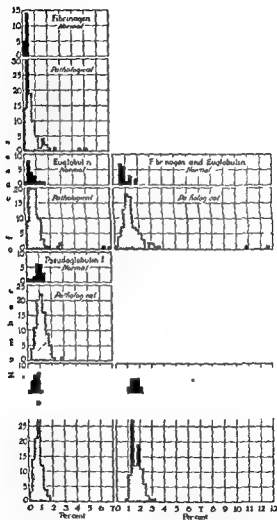


FIG. 108 — Distribution of normal and pathological plasma protein values

While the albumin showed diminution, the total globulin, including fibrinogen showed significant increase the mean being 3.47 per cent  $\pm 0.11$  as *versus* the normal  $2.59 \pm 0.05$ . The difference is significant the ratio of the difference to the probable error of the difference being 7.3. The coefficient of variation for the pathological group is more than three times larger than for the normal.

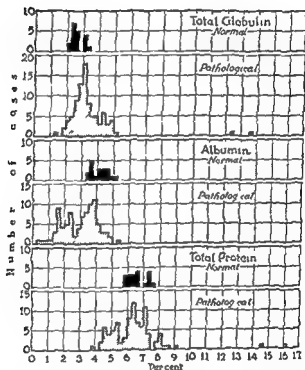


FIG. 107 — Distribution of normal and pathological plasma protein values

TABLE 34 — Summary of results

gen and albumin vary usually in opposite directions. The authors' material both in this and subsequent chapters in regard to these two large fractions amply demonstrates an independent variation, the euglobulin-fibrinogen fraction frequently being increased independently of any alteration of albumin. The reader will have noticed that the authors have refrained from the use of the term

nephrosis. As an instance of proteinuria in renal insufficiency with uremia they offer the findings in a young man from the Peter Bent Brigham Hospital (Med No 25816) James R., whom they studied in some detail during the last fifteen days of his life

albumin

In toxemia and eclampsia of pregnancy on urines obtained from the

failure the following observation may be cited as an instance where

The low albumin with rare exceptions is due to an extraneous process heavy renal leakage but not a part of the other intrinsic plasma changes

The euglobulin and fibrinogen present a different situation Fig 108 reveals a marked skewness in the distribution of the observations this is true also for the normal euglobulin The pathological means  $0.747 \pm 0.007$  for fibrinogen and  $0.874 \pm 0.075$  for euglobulin both show standard deviations larger than the normal and correspondingly high coefficients of variation 107 for fibrinogen and 120 for euglobulin Both means were higher than the normal means A more adequate presentation of these values is given by Table 73 comparing the normal and pathological

TABLE 73 DISTRIBUTION OF FIBRINOGEN AND EUGLOBULIN VALUES IN NORMAL AND PATHOLOGICAL PLASMA ACCORDING TO QUANTILES THE VALUES REPRESENT GRAMS PROTEIN PER 100 CC PLASMA

	Min	25 per cent	50 per cent	75 per cent	Max
<i>Fibrinogen</i>					
Normal	0.16	0.25	0.29	0.37	0.40
Pathological	0.03	0.19	0.39	0.77	5.19
<i>Euglobulin</i>					
Normal	0.20	0.37	0.51	0.78	1.64
Pathological	0.13	0.28	0.56	0.85	7.41

The fact that the total protein both normally and pathologically shows lower

sarily brings

in a reciprocal manner

be the case with the two pseudoglobulins For the other fractions we believe the question is to be answered in the negative The relative constancy of the total protein depends on the fact that around the highly constant pseudoglobulins the euglobulin fibrino-

gen and albumin vary usually in opposite directions. The authors' material both in this and subsequent chapters in regard to these two large fractions amply demonstrates an independent variation, the euglobulin fibrinogen fraction frequently being increased independently of any alteration of albumin. The reader will have noticed that the authors have refrained from the use of the term

nephrosis. As an instance of proteinuria in renal insufficiency with uremia they offer the findings in a young man from the Peter Bent Brigham Hospital (Med No 25816), James R., whom they studied in some detail during the last fifteen days of his life

albumin

THE AUTHORS HAVE NOT EXTENSIVELY STUDIED PROTEINURIA DUE TO HEART FAILURE. THE FOLLOWING OBSERVATION MAY BE CITED AS AN INSTANCE.



The material in preceding sections showed great variability in the relative amounts of albumin and globulin. This was brought

In the uremic patient just described no such experiment could be carried out. In patient Grace C-n, discussed in next section and in Table 76, with definitely reduced renal function, the level of protein metabolism was varied greatly, this was followed by corresponding changes in protein elimination but the globulin fraction varied two-sixths only from its maximum relative amount. Other observations pointing in same direction support the conclusion that in renal insufficiency the variability of the protein composition of the urine is less than when renal function is preserved.

TABLE 74—COMPARISON OF THE SOLUBILITY OF URINARY PROTEIN NORMAL PLASMA PROTEIN AND PATHOLOGICAL PLASMA PROTEIN IN TERMS OF PERCENTAGE UNPRECIPITATED PROTEIN AT DIFFERENT CONCENTRATIONS OF SODIUM SULPHATE. THE PLASMA FIGURES ARE CALCULATED FROM TABLES 69 AND 70

M concentration Na <sub>2</sub> SO <sub>4</sub>	Urine		Plasma	
	Mean $\pm$ P.E.	$\sigma \pm$ P.E.	Normal	Pathological
0.75	97.9 $\pm$ 0.33	2.78 $\pm$ 0.23	95.6	88.4
1.00	94.3 $\pm$ 0.73	6.09 $\pm$ 0.31	85.4	74.8
1.25	84.9 $\pm$ 1.46	12.23 $\pm$ 1.03	71.3	57.3
1.55	76.5 $\pm$ 1.62	14.60 $\pm$ 1.14	61.0	45.3
1.70	75.4 $\pm$ 1.97	12.06 $\pm$ 1.36	55.5	35.1

Three precipitation curves for urinary proteins from 1 individual were given in Fig. 105. In Table 74 are given the mean values and standard deviations for 38 different curves, 19 of which also included precipitation with 1.7 M Na<sub>2</sub>SO<sub>4</sub>. The curves were obtained from 23 individuals with different types of renal disease. It is evidently impractical with urinary protein of widely different concentrations to use absolute values for means or curves. The values of the different fractions instead are expressed in percentage of total protein. Table 74 gives in percentage of the total protein the amount still unprecipitated at each concentration of sodium sulphate. The values for the normal proteins with the normal plasma are given in the same manner and included in Table 74 in its last two columns. Inspection of the individual cases in which plasma and urine were studied con-

After the previous discussion of the variability in composition of urinary protein it is worth realizing that a general pattern may nevertheless be recognized, sufficiently characteristic to be compared with the corresponding pattern of the blood. On comparison one finds the standard deviations of the urinary fractions to be of the same order of magnitude as those of the blood fractions. The coefficients of variation if calculated not for the unprecipitated protein, but for the precipitated amounts at each salt concentration, range much as in the plasma from about 130 for fibrinogen step by step down to 50.

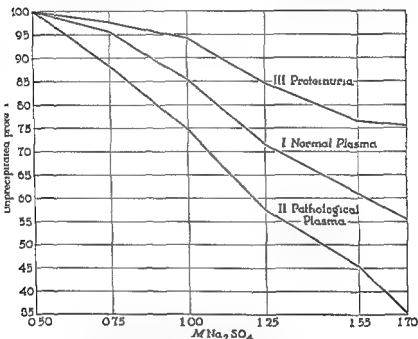


FIG. 109 — Comparison of precipitation curves for urinary proteins: normal plasma proteins and pathological plasma proteins.

Attempting to express what the difference between the urine

the difference between the proteinuria curve and the pathological

plasma curve means that in equal amounts of urinary and plasma proteins 1 mg of each fraction of the former will be represented by the following number of milligrams of the same fraction in the latter Fibrinogen 1 to 5.5 eugl

1 to 1.9 pseudoglobulin II 1 to

one might say that albumin will

proximately ten times easier than fibrinogen (or a plasma protein of the solubility of normal fibrinogen) and so on. The composition of urinary protein usually might have little to do with the alteration of the filtering membrane or with the magnitude of the plasma fraction; it is more closely dependent upon physical properties of the plasma proteins such as molecular weight viscosity or other factors. One possible exception exists namely amyloidosis. In 1 subject this diagnosis was made the ratio between urinary and plasma protein came out as follows fraction by fraction Fibrinogen 1 to 1.2 euglobulin 1 to 0.8 pseudoglobulin I 1 to 1.5 pseudoglobulin II 1 to 1.1 and albumin 1 to 0.8

One type of curve frequently observed in nephrosis or long standing nephritis shall be mentioned. The curve first runs almost flat with a sudden drop in the area of pseudoglobulin I (M 1 to 1.2) whereafter nothing more comes down within the range of 1.2 to 1.5 running absolutely horizontal even on

the three curves of Fig 109 in this area deserves comment the urinary protein curve running almost horizontally the pathological plasma curve being the steepest the normal plasma falling between. It seemed important to prove that these differences are statistically significant. The means of the amounts precipitated between 1.5 and 1.7 M salt concentration from normal and pathological plasmas were 363 mg  $\pm$  26 and 311 mg  $\pm$  26. The ratio between the difference of the difference was 5.1. Since the plasma curves thus meet

## A PROTEIN CREATININE TEST FOR GLOMERULAR PROTEIN LEAKAGE

It is not known how to correlate albuminuria with other phenomena intrinsic with a diseased kidney. It is not likely that a morbid sign as prominent as albuminuria cannot in some way be correlated with reduced renal function. Surely in essential hypertension albuminuria occurs or increases with deterioration of function. Generally it might be stated that though heavy albu

minuria may or may not be present from a diseased kidney with preserved function, there is no renal insufficiency without marked albuminuria. This statement should be guarded by confining it to renal insufficiency of glomerular or vascular origin, though the majority of instances of renal insufficiency has this pathogenesis, there are at least two groups of exceptions and the authors have observed instances of both (1) Renal insufficiency in myeloma and Bence-Jones proteinuria without albuminuria, and (2) renal insufficiency in hydronephrosis and increased back pressure in prostatic hypertrophy. Since as it has been shown in Tables 66 and 67 (pages 493 and 494), the concentration of urinary protein has to be correlated with the rate of diuresis or rather with the degree of concentration of the urine equally heavy albuminuria should not be expected in isosthenuria as in a highly concentrated urine. This expectation, reasonable as it may appear, needs to be tested because of the singular position occupied by proteinuria. While other compounds are being retained proteins are being spilled. Rowntree and Geraughty were uncertain which would be the fate of phenolsulphonephthalein whether it was going to leak through the diseased kidney in increased amount like protein or be retained like urea.

We know that proteinuria cannot be correlated with the protein concentration of the plasma nor even with its content of albumin, though it is closely correlated with the protein intake. We also know that the hourly protein elimination may be as constant as the creatinine output and independent of diuresis. The authors have concluded that the protein leakage takes place in the glomeruli, a conclusion supported by Bieter's observation<sup>7</sup> that proteinuria cannot be produced in the aglomerular kidney. Thus it becomes natural to attempt a correlation of proteinuria with glomerular function. This may be done by the use of the rate of glomerular filtration determined according to Rehberg. It is plausible that with most glomeruli functioning more protein might be lost than if 70 to 80 per cent of the filtering structures have been wiped out. The authors have determined the amount of protein in the urine sample of the Rehberg test. They have attempted to correlate the one hour protein elimination with the rate of glomerular filtration and found no correlation. Such a correlation would have indicated a somewhat identical degree of glomerular leakage in all diseased kidneys. The authors have further calculated the concentration of the eliminated protein in the glomerular filtrate in the following way. In Rehberg's creatinine test one arrives at the minute filtration from the concentration index for creatinine and the volume of urine. They arrive at the intracapsular concentration of the protein from the amount of urinary protein and the volume of glomerular filtrate, simultaneously determined by the creatinine test, or, more simply,

from the concentration of the urinary protein and the concentration index of the creatinine

TABLE 75 — PROTEIN LEAKAGE IN GLOMERULAR FILTRATE CALCULATED FROM THE PROTEIN-CREATININE TEST

No	Filtration rate cc per min	Urine volume cc per hr	Protein concentration mg per 100 cc	Protein elimination mg per hr	Protein in glomerular filtrate mg per 100 cc	Albumin per cent of total protein	Creatinine excreted on mg per hr	Concentration ratio for creatinine
1	260	200	33	64	0.4		642	78
2	169	47	416	196	1.9	75.2	329	316
3	143	45	195	89	1.0	86.12	412	160
4	140	140	159	223	2.7		280	53
5	139	190	68	139	1.6		399	44
6	132	46	825	372	4.7	85.2	287	177
7	121	285	24	68	0.9		578	26
8	114	17	3516	598	8.8	83.0	323	402
9	111	96	422	405	6.1	77.3	376	70
10	109	14	4078	571	8.8	83.0	302	466
11	108	81	384	311	4.8	65.1	360	60
12	94	40	518	207	3.7	69.5	190	141
13	84	164	469	769	14.6		505	■
14	85	112	24	27	0.6	61.6	196	46
15	49	97	260	253	8.6	65.6	215	30
16	48	176	453	793	27.6	68.7	273	16
17	31	55	500	275	14.8		51	34
18	26	55	1050	578	37.2	■ 8	121	28
19	24	195	379	739	51.7		140	7
20	23	217	270	596	41.9	74.8	156	7
21	23	38	1875	713	51.0	65.2	82	37
22	22	26	1246	561	23.8		88	52
23	19	216	272	588	52.1	60.3	112	5
24	18	76	197	150	13.8		112	14
25	10	100	195	195	33.1	66.7	86	6
26	7	46	551	254	59.4		44	9
27	6	83	97	85	25.5		57	4
28	4	35	197	70	28.6		34	7
<i>Additional</i>								
29	6	37	954	359	100.0		39	10
30	6	52	319	166	49.8		49	6
31	132	37	326	121	1.5		277	215
32	7	97	553	536	106.0		63	4
■	36	54	578	312	14.4		170	40
34	98	22	117	26	0.9		354	264
35	20	30	1659	498	42.3		80	39
36	73	290	34	99	2.1	76.0	350	16
37	77	96	98	94	2.0	98.5	160	48

The results of 28 such protein-creatinine tests are compiled in some detail in Table 75. The material shows a wide spread with filtration-rates from 260 to 4 cc per minute, only one big hole

occurring with no rates between 85 and 149 cc. Eleven of the 28 observations had filtration rates above 100 cc and 12 below 40 cc. The one hour urinary volume varied between 280 and 14 cc, the protein concentration between 40.8 and 24 mg per 100 cc urine and the protein output between 793 and 27 mg per hour. The calculation of the protein concentration in the glomerular filtrate renders values between 0.4 and 59.4 mg protein per 100 cc. Six of the 28 observations gave values lower than 2 mg per 100 cc and 11 gave values above 20 mg. There exists a marked negative

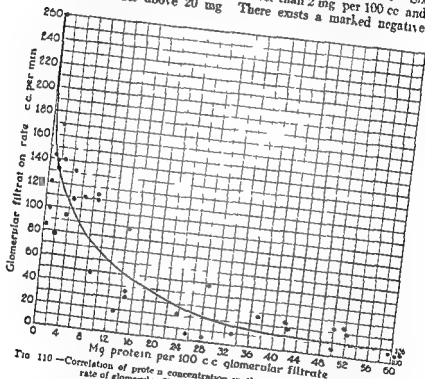


FIG 110—Correlation of protein concentration in the glomerular filtrate against rate of glomerular filtrate on Proteo-creatinine test

correlation between protein concentration and filtration rate as demonstrated by Fig 110\*. Thus as large numbers of renal units cease to function the remaining filtering units become altered in such a way that they allow protein to pass in increased concentration. The absolute figures obtained by this calculation are surprisingly low lower than the protein concentration in edematous fluids for which particularly when edema is increasing one might assume

\* A few more observations have been appended to Table 75 and also laid on Fig 110. They confirm the findings in the first tests.

very slight or no concentration of the transudating fluid to take place. The figures resemble the protein content of cerebrospinal fluid.

Observations 8, 10 and 21 in Table 75 were made on the same patient and at the same time.

filtrate from 8.8 to 51 mg per 100 cc

This might be written

$$\frac{P_u}{t} \times \frac{V}{F} \times 100 = P_r$$

where  $P_u$  = urinary protein in mg per 100 cc

$t$  = time of experiment (60 minutes)

$V$  = urinary volume

$F$  = glomerular filtrate cc per minute

$P_r$  = protein mg per 100 cc of glomerular filtrate

Or more simply

$$\frac{P_u}{C_u} = P_r$$

hence

that

$$F = \frac{C_u}{C_s} \times t \quad (\text{Rehberg's equation})$$

In the accompanying figure we have plotted  $F$  (ordinate) against  $P_r$  (abscissa).

$$F = (f) P_r$$

may also be written

$$\frac{C_u}{C_s} \times \frac{V}{t} = (f) \frac{P_u}{C_u}$$

in which the term  $\left( \frac{C_u}{C_s} \right)$  appears on both sides of the equation once in the

1

determine quantitatively

This behavior in proteinuria increasing permeability to protein with decreasing amount of functioning renal tissue we have been tempted to interpret as the most important renal factor in proteinuria. How is this factor influenced by the various hematogenous factors? Some observations are presented on the effects of the

most important of these factors, the level of the protein intake Miss Grace C-n (Table 76), with chronic nephritis and secondary hypertension of two years' duration, during the first year presenting marked and persistent edema, during the second year in good general condition, in the course of nine days was submitted to four protein-creatinine tests on high and low protein diets, and again on high protein diet. Table 76 also includes an earlier test on high protein diet twenty days prior to the first test of the series. Table 76

concentration in the glomerular filtrate show very large variations, the minute filtration four and a half times its lowest value and the protein concentration a little more than three times. From the table is clearly illustrated that variations in filtration-rate influence the value for the protein concentration in the filtrate to a greater extent than variations in the hourly protein output or in the level of protein intake. This fact ordinarily is somewhat hidden by the mode of expression filtration-rate being given per minute and protein output per sixty minutes. The authors believe that the long metabolism experiments which constitute the first part of this treatise may be advantageously replaced by a series of protein-creatinine tests. It should be possible in this way to accumulate uniform material for an interpretation of proteinuria better founded than the first attempt here offered.

TABLE 76.—INFLUENCE OF VARYING LEVELS OF PROTEIN INTAKE UPON THE PROTEIN-CREATININE TEST

Experimental condition	Date	Rate of glomerular filtration cc per min	Protein excretion mg per hr	Protein in glomerular filtrate rate mg per 100 cc
Grace C-n				
Diet				
High protein	5-21	84	769	11.6
High protein	6-10	44	793	24.5
Low protein	6-12	19	584	52.1
Low protein	6-13	23	546	41.9
High protein	6-18	24	735	51.7
Mrs. B-y				
Diet				
Ordinary	4-9	139	123	1.55
Moderately high protein	5-24	104	311	4.77
High protein	6-14	111	405	6.07
Low protein	6-22	91	207	3.69

The variations in filtration-rate deserve independent discussion. The decline in rate in Grace C-n (Table 76) does not indicate that



the patient was rapidly progressing toward uremia. Her subjective condition was most satisfactory. She traveled and played nine holes of golf, and there was no symptomatic correlation with the filtration-rate. The patient was not hospitalized during the experiments, only spending the forenoons on a bed in the laboratory. It is amazing to find a drop from 48 to 19 cc. minute filtration in two days following the change from high to low protein diet.\* In this connection one recalls the clinical experience that chronic nephritics frequently do poorly when hospitalized on low protein diet but improve when they return home to more liberal dietary habits. The authors do not interpret the rapid changes in Grace C-n as indicating a corresponding anatomical deterioration, but see in

early the increase from 29 to 52 mg. per 100 cc. on change from high to low protein diet and marked decrease in protein output. Can this changed permeability for protein also be interpreted on the basis of alteration in function without change in structure?

One interpretation which suggests itself from the correlation of the row of figures for protein output with either one of the rows for minute filtration or protein concentration in the filtrate is that the proteinuria is entirely hematogenous, like the creatinuria, a certain amount of the blood proteins being so altered that they escape through the kidney, in high or low concentration, according to the functional capacity of the kidney—an idea in accord with Epstein. The authors hesitate unreservedly to accept this interpretation, though their discussion in the next and last section leads in this general direction. In addition at least two renal factors might be considered as partially influencing these phenomena, the rate of blood flow through the capillaries and the blood-pressure in the capillary loops of the tuft. That this pressure

tion may be carried on

2 1 0 0 0

\* Rehberg has correlated changes in filtration rate with changes in concentration of the total plasma proteins. In Grace C-n the protein changes are sufficiently complicated to discourage the pursuit.

Thus we find that in the protein-creatinine test the level of the protein intake may greatly influence the result, and evidently in an irregular and possibly unpredictable way depending on the

madvisable even as a temporary measure and others where it will appear impossible to the patient to take such a diet

The percentage distribution of albumin and globulin in the protein-creatinine test should be referred to briefly Table 75 shows in a general way a high globulin content in all cases with reduced filtration-rate and high protein concentration in the glomerular filtrate, while the globulin content may be high or low in instances of high filtration-rate and low protein concentration in the glomerular fluid This is in harmony with the discussion in the preceding section

**Summary and Discussion** —In the experiments reported on the preceding pages it has been easy to demonstrate the rôle of hemato-genous factors in proteinuria and difficult to be sure of renal factors We have seen

diet and promptly come  
all appearance as a pur  
irritation or damage

This response to altered protein intake did not occur in an untreated patient with myxedema and heavy proteinuria, but on administration of desiccated thyroid during high diet the patient showed increased proteinuria for nine to ten days, in lieu of increased nitrogen elimination, ordinarily observed and interpreted as due to mobilization of stored protein

Proteinuria was found temporarily to increase on change from resting recumbent position to active walking about, and to decrease upon the administration of sodium citrate, while sodium chloride and calcium chloride were without effect Injection of arsphen-

mine likewise had no effect. Fever increased the loss of protein as did blood transfusion.

High diuresis and transition to low diuresis had no effect upon protein elimination but sudden transition from low to high diuresis was apt to bring about a slight and transitory increase. Feeding large amounts of urea might or might not cause a moderate increase in protein elimination.

The facts are in harmony with the assumption of the glomeruli as the foci of protein leakage. The behavior of the protein elimination during dilution-concentration tests particularly corroborates the assumption. Combination of the rate of protein elimination with the rate of glomerular filtration as determined by Rehberg's creatinine test permits calculation of the protein concentration in the glomerular filtrate and offers a measure of the degree of glomerular leakage. Intracapsular protein concentrations thus arrived at exhibit marked negative correlations with the rate of glomerular filtration. The rate of glomerular filtration influences the values for the intracapsular protein concentrations more than does the level of protein intake.

Further discussion of proteinuria necessitates consideration of the plasma proteins. Comparison of normal and abnormal plasmas reveals certain facts in regard to the biological behavior of the separate protein fractions. Arranged according to decreasing solubility (albumin, pseudoglobulin II, pseudoglobulin I, euglobulin and fibrinogen) they are at the same time arranged essentially according to their order of magnitude in normal plasma (albumin, 100, pseudoglobulin I, 23, pseudoglobulin II, 17, euglobulin, 17 and fibrinogen, 7) and inversely according to variability of concentration (coefficient of variation under abnormal conditions: albumin, 37, pseudoglobulin I, 35, pseudoglobulin II, 35.5, fibrinogen, 107 and euglobulin, 120).

As shown by other investigators they are as first arranged also arranged according to increasing molecular weights, according to decreasing osmotic effect and as far as known according to decreasing base binding capacity.

According to their behavior under pathological conditions the fractions may be combined into three groups: albumin, the pseudoglobulins and the euglobulin-fibrinogen.

There is no reason to assume that low albumin could be a failure of normal synthesis, all evidence pointing to an extraneous cause in the form of leaking kidneys. In myeloma only (page 534 A G) has pathological suppression of plasma albumin been observed.

unassociated with loss of albumin through the urine. In albumin depletion rapid albumin synthesis following high protein feeding may occur, but it is not clear why this is only rarely observed — rather slow increase being the rule. An almost complete albumin depletion is compatible with life but as far as known always accompanied by large and unmanageable edema.<sup>10</sup> Even in this situation sufficient water is retained in the vascular system to protect against any marked polycythemia — a situation assured by the hydration

min extraneously decreased the pseudoglobulins constitute the most constant factor of the plasma. They participate neither in the reactions of the albumin nor of the euglobulin fibrinogen.

The euglobulin fibrinogen consisting of the largest molecular aggregates of the plasma show by far the greatest instability. For fibrinogen the known function of which consists in its easy conversion into fibrin this might be essential. The euglobulin and fibrinogen vary together or independently of each other but hardly reciprocally. We have sometimes found one or the other decreased, mostly both are increased and the range over which they

Experiments have demonstrated the correlation of decreased stability of the blood suspension with increased globulin fibrinogen content. The relationship between euglobulin fibrinogen content and the level of protein intake though possibly equally marked under a variety of conditions has been demonstrated in renal disease only. In this condition the euglobulin fibrinogen content is markedly increased independently of the protein intake but especially high values are observed where the protein intake has been maintained high and spectacular diminutions follow within two to four days upon the discontinuation of the high diet.

Thus at least three entities with different biological behavior are distinguishable in the plasma proteins. The last discussed group made up of large aggregates possesses the least stability. As to the mode of the building up of these groups the observations allow little insight into the synthetic machinery. A few observations at Woods Hole and scattered reminiscences from the literature

have given the impression that globulin is phylogenetically the oldest blood protein. Is it also the mother substance for the smaller and more stable plasma proteins or is each the result of separate synthesis? Certain behavior of the urinary proteins suggests the latter alternative.

It has long been known that the qualitative and quantitative composition of the urinary proteins does not reflect the proportions of the proteins in the plasma. It might be assumed that the gross difference in composition is due to certain physical rather than chemical properties of the protein fractions manifesting themselves in contact with a glomerular membrane no longer completely impermeable to colloids of the order of magnitude of the normal plasma proteins. As to these properties of the proteins and as to the changes in the glomeruli nothing direct can be said. Unlike the situation in Bence-Jones proteinuria (see page 543) we deal in ordinary proteinuria with a graded permeability difficult to define further. The authors have suggested that the proteinuria resulting from this abnormal permeability might be influenced by the rate of glomerular blood flow and by variations in glomerular blood pressure. The calculations based upon the protein-creatinine test suggest a wide range in the degree of leakage and particularly indicate a sur-  
" well preserved  
ular leakage is  
to the propor  
tions of the plasma proteins though even here the difference ■

A difference from the situation in which kidney function is preserved. Here the urinary proteins do not always differ from what is observed in renal insufficiency but the pattern is not fixed and might be varied within wide limits not according to the apparent composition of the plasma but according to the intensity with which the plasma proteins are being built up under the influence of a high level of protein assimilation.

Two types of variations have been observed. In the first type most frequently observed in the authors material the urinary protein during ordinary or low protein diet may consist almost entirely of albumin in addition to the other plasma fractions. On high diet the albumin fraction may be relatively increased and the other plasma fractions may be relatively decreased. In the second type of variation the urinary protein during ordinary or low protein diet may consist almost entirely of albumin in addition to the other plasma fractions. On high diet the albumin fraction may be relatively increased and the other plasma fractions may be relatively decreased.

\* See Howe in *Phys. of Rev.* vol. II

increase—the reason for the authors' caution not to interpret the response to fever necessarily as altogether renal.

In the second type the urinary proteins show the reverse response to high diet, the albumin increases more than the other fractions. This has been observed in severe protein depletion and marked positive nitrogen balance. It was seen also in one instance, tenta-

It remains to discuss the significance of the solubility of the urinary albumin as compared with the albumin in normal and pathological plasma. In the urine from a severe nephritic with high glomerular permeability, as defined above, the slope of the salting-out curve between 1.55 and 1.7 M  $\text{Na}_2\text{SO}_4$  may differ very little from the slope in normal or nephritic plasma. The curve of pathological plasma frequently is steeper than that of normal plasma. The salting-out curve from urine in cases of nephrosis or chronic nephritis with fairly normal function and low glomerular permeability for protein differs from the preceding ones by its horizontal course. This means that under the latter circumstances the urinary albumin has a higher solubility than the plasma albumin, indicating that it consists of smaller molecules. It is characteristic of the urinary protein in some cases of nephrosis and nephritis to contain two fractions chiefly of widely different solubility, a small amount precipitating as pseudoglobulin I and the remainder still fully soluble in 1.7 M concentration of  $\text{Na}_2\text{SO}_4$ , the highest concentration obtainable with this salt. Where with  $(\text{NH}_4)_2\text{SO}_4$  this albumin starts to come down has not been investigated, for lack of a method that the authors dared to trust for this purpose.

This characteristic of urinary albumin gives the clue to the correlation of proteinuria with protein intake instead of with plasma proteins. The following interpretation is offered. The albumin fraction of the plasma includes molecules of different solubility and size. Whether this holds also for the other fractions is not clear. On high protein intake, particularly in positive nitrogen balance, these smaller molecules are markedly increased. Whether this means that under conditions of rapid protein synthesis they are discharged into the circulation before they have been built up to full

size the authors do not know. It is not plausible that after they have entered the circulation they become coupled together to form larger aggregates neither is it plausible that they are just passing through the blood stream to be used as building stones in other tissues. On discontinuation of high protein intake their amount rapidly and markedly decreases in the plasma. On slight damage to the glomerular capillaries these small molecules will be the first ones to pass through the filtering membrane. This constitutes a selective drain on the plasma albumin which deprived of its most soluble molecules shows a steeper slope between 150 and 17 M Na- $\text{SO}_4$  than normal plasma. Under the influence of this drain the plasma protein synthesis becomes accelerated small molecules are released and rapidly removed through the kidney a vicious circle is set up and in spite of high protein intake the albumin regeneration remains retarded. With experimental and clinical evidence supporting this course of events the authors have not been convinced about the necessity to assume with Epstein the operation of an erroneous protein synthesis for the pathogenetic explanation of nephrosis. Whether mild glomerular injury with low capillary permeability for protein causing a prolonged and selective drain on the plasma albumin alone offers an adequate explanation of the complicated clinical picture called nephrosis—on this point the authors' experiments give no answer.

## APPENDIX

It might be a procedure open to criticism to report experiments as comprehensive as those above without appending a brief clinical account of the patients studied.

CASE 1—Mr. B., aged forty-four years Italian workman entered the Peter Bent Brigham Hospital (Med. No. 25754) for the third time April 23 1924.

Nocturia in 1923 severe left ple pneumonia January 1924. Transient swelling of ankles March 1924 2000 cc fluid removed from left chest about the same time the same amount removed in June 1924 persistent edema of legs ever since also pain in left side of chest more or less constant. Admitted to the Peter Bent Brigham Hospital August 20 1924.

phthalein tests varied from 40 to 50 per cent.

Took calcium chloride at home edema almost disappeared weight

reported. Condition otherwise as before. Discharged February 26 1925. Remained in bed at home save for occasional short walks. Weight increased from 148 to 172 pounds.

Readmitted April 23 1925. Discharged November 20 1925. Height 162 cm. Tonsils not enlarged or diseased. Symmetrical expansion of

or below 130/90

This history calls for little comment. In describing the experiments on page 47b the patient was presented as an instance of nephrosis. The clinical picture at the time of the experiments is well characterized by this name. Here we are not concerned about the ultimate outcome of the disease or the finer histological appearance of the glomeruli. But attention shall be called to two facts, one clinical and one of laboratory nature. (1) There was before the reported experiments but after the patient had been sick for more than a year already a short period when the blood pressure was elevated and this period was terminated by pseudoureimic convulsions and their sequelæ. (2) There was considerable variability in the results of the phenolsulphonephthalein test. On increased protein intake the test jumped from 2.5 to 40 per cent. The authors wish to correlate this with the behavior of the Richberg test in *Grace C. a.* (Table 7b page 513).



weeks in bed only to reappear more marked after acute rhinitis with slight  
 for the first time

some granular casts but no rec

The non-  
 t gave the  
 limination  
 ed protein

The clinical picture and functional performance at the time of  
 At the

CASE 3—Edwin T. r. aged twenty five years, an English born grocery  
 clerk, entered the Peter Bent Brigham Hospital (Med. No. 26074), on

because of albuminuria. Entirely unaware of any trouble with the kidneys  
 for the insurance. January 18, 1925 severe attack of grippe with sore  
 throat and hoarseness. Nine days later face began to swell the swelling  
 gradually extending all over the body. In the county hospital swelling

Edema increased,  
 its apparent cause  
 disappeared com-  
 1926 was getting  
 anything, feeling

The remark as to diagnosis under the preceding history seems applicable even to this patient

CASE 4—Mr. H., aged fifty-two years, a German-born salesman,  
 was first seen by me in 1925. He had been ill for some time,  
 and had been in the hospital for some time. He had been  
 in the hospital for some time, and had been in the hospital for  
 some time. He had been in the hospital for some time, and had  
 been in the hospital for some time. He had been in the hospital  
 for some time, and had been in the hospital for some time.

occasional hyaline and granular casts and white cells; no red cells ever demonstrated with certainty.

The patient died May 27, 1927, in a sanatorium. His last months of life were characterized by persistent vomiting, the cause of which is not

An instance which may well be called nephrosis in chronic tuberculosis and where amyloidosis is generally assumed to exist but not always found

Case 5 — 37 m T. C. a former coal miner came to the Clin. at

condition that might be a precursor of an acute or a chronic nephritis. He reports no edema of eyelids or ankles, no nocturia, no polyuria and never observed blood in the urine.

Physical examination reveals a normal male normal

cent

Discharged November 18, 1934. At that time only a trace of albumin was present in the urine and the phenolsulphonephthalein test was 60 per cent for two hours.

Patient returned for examination at frequent intervals and at these times his urine usually showed albumin casts and white blood cells.

He was in the hospital for further observation from January 22 to 30. 1935. On admission few casts, no normal. He ut no edema weather so

did not work after the onset of winter.

Readmitted for observation July 7 and discharged July 12, 1935.

Physical

Murphy

2+ to 3+

Blood ure

hours. Ophthalmoscopic examination. Disk round, margins sharp, vessels

vessels

Patient reported occasional puffiness of face and eyelids otherwise no symptoms of nephritis.

forward

This case should not be confused with syphilitic nephrosis as that picture frequently has been described. Neither is there any reason to correlate the urinary finding with the antisyphilitic treatment nor with the small amount of Hg treatment that the patient might have received. In the absence of other symptoms of mercurialism one should have expected the albuminuria if due to mercury rapidly to disappear on the discontinuation of treatment. This otherwise symptom free albuminuria in syphilis of which we observed a second instance at the Boston dispensary is an obscure condition though it has long been known.\*

CASE 7—Mrs. A-c aged fifty five years Norwegian born housewife entered at 11 a.m. on 11/11/52 on April 1, 1976 & expired of

th scales fine like  
Slight edema of  
Heart on 6-foot

After four years February 13 1930 the patient was gone over in detail. She had been taking 2 grains desiccated thyroid twice daily regularly. The basal metabolic rate was +4. Blood pressure 140/76. Hemoglobin 90 red cells  $\pm 860,000$ . Ophthalmoscopic examination suggested only a beginning arteriosclerosis of the retinal vessels. Urine contained no albumin. The plasma protein which was depleted in 1926 (see Fig. 106) now was 8 per cent with the following composition: 3.87 gm total globulin, pseudoglobulin II or I 1 per cent and fibrinogen 1 per cent; this fraction thus still differing from normal values.

In 3 of the first 4 cases of this series the basal metabolic rate was studied and found below normal. In this patient the clinical picture is entirely different from that of the preceding cases of nephrosis. Here is a picture of asthenia chiefly, which in combina-

of the present authors (Scriver) observed no influence of thyroid medication upon the albuminuria of true nephrosis, at variance with what has been described by Epstein\*.

to suppression relieved by oral administration of sodium chloride 10 g daily for 10 weeks.

\* Lewis D. H. and Scriver W. de M. *Ann Int Med* 3: 66-8, 1928.

The patient presented generalized marked edema the breathing was difficult he was able to move with aid only. Mentally he was somewhat cloudy. Weight 87.4 kg. There was a 5 cm large carbuncle on the back of the neck which was incised and drained. The size of the heart was

115 mm. May 21 was incised May 22 - Discharge Acute or subacute nephritis

Instead of discussing the diagnosis which seems superfluous the authors want to remind the reader of what Addison calls renal failure casts. Epithelial casts were repeatedly observed in the urine from this patient but the broad dark casts in which interest has been revived through Addison's studies were not described perhaps because they did not look for them. While earlier clinicians mentioned them in contracted kidneys chiefly Addison has observed them also in subacute forms.

That isosthenuria (specific gravity around 1.011) does not occur in renal failure of acute nephritis has been brought out by Vollard and is illustrated in this patient with specific gravity of 1.017 to 1.021. But the concentration accomplished by the kidney is estimated too high if based on the specific gravity since the protein content of the urine was high between 1.8 and 2.9 per cent which corresponds to a specific gravity of the protein solution alone of 1.005 to 1.008. This taken into account the kidneys produced a urine but little better than isosthenuria.

\* Addison T. J. Am. Med. Assn. 84: 1013-1015, 1925.

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CHAPTER XXXI  
BENCE-JONES PROTEINURIA \*

By GRACE MEDEY, PH D  
WITH  
THE PARTIAL COLLABORATION OF  
HILDING BERGLUND, M D  
AND  
THE TECHNICAL ASSISTANCE OF  
MARY R. NEEVEY, B S

CHEMICAL CHARACTERISTICS OF BENCE-JONES PROTEIN

**Conditions Affecting Tests for Bence Jones Proteins** The usual test for the demonstration of Bence-Jones protein in urine is a modification of the heat and acetic acid test as described by Magath (page 441). The urine is slightly acidified with acetic acid and

temperatures is incomplete rendering the identification of the protein less simple. The difficulty is often ascribed to the admixture of

the conditions of the experiment. These conditions are elucidated by the behavior of Bence-Jones protein in salt free solution.

Applying their studies to salt free solutions of the protein

\* Aided by a grant from the Research Fund of the Graduate Medical School of the University of Minnesota.

that in strongly alkaline solutions no precipitation is discernible. They apparently did not observe that at low degrees of alkalinity the protein behaves very much as in slightly acid solution the coagulation appearing at a somewhat higher temperature with a tendency to redissolve as the boiling point is approached.

Magnus Levy<sup>28</sup> was the first to recognize that the characteristic behavior of Bence-Jones protein depends upon the simultaneous presence of other urinary constituents. He considered urea as the compound of chief importance. Hopkins and Savory confirmed the role

of urea

in low c

solubility of the protein at high temperatures. Monovalent salts like NaCl have a slight effect. The dissolving power increases in neutral (very faintly acid) solution with increase of valency of either the acid or the basic constituent. For complete clearing at the boiling point at least dibasic ions are essential. In higher concentrations the same salts are effective salting out agents. When magnesium sulphate is present at approximately one-half saturation the heat coagulum induced at 50° C no longer completely dissolves at 100° C. When about two thirds saturation is reached the coagulum does not dissolve at all. Ammonium sulphate has similar action.

Equal to the salt content in importance is the hydrogen ion concentration. Hopkins and Savory worked at three different pH: one neutral or slightly acid, a second more acid obtained by adding 1 drop of glacial acetic acid to 200 cc of the neutral fluid, and the third an alkaline solution consisting of the original dialyzed material. They state that it was faintly alkaline to litmus. Malengreau<sup>29</sup> who more extensively studied the influence of different pH upon the salt effect states that the acidity of Hopkins and Savory's acid solution was scarcely sufficient to bring it outside of the isoelectric zone. Hopkins and Savory found the dissolving action in acid solution to be favored by the increasing valency of the positive ion and in alkaline solution by the valency of the negative ion. Malengreau's observations led him to the opposite conclusion. All are agreed that some association exists between salt and protein and that the physical properties are markedly different at high and at low temperatures because of differences in this association or in the ionization of the resulting compound. Various values for the isoelectric point have been reported. Hewitt<sup>15, 16</sup> at between pH 5.5 and 6. Willheim<sup>47</sup> at pH 4.05 to 4.75 and Svedberg<sup>33, 39</sup> at pH 5.18 to 5.9.

Considering the variability of urines with respect to hydrogen ion concentration and salt content all specimens cannot be expected to show a complete reversibility of the solubility without adjust

ment of one or both factors.<sup>1</sup> Possibly the most successful attempt at such an adjustment has been described by Osgood and Haskins.<sup>29</sup> To 5 cc. of urine in a test-tube they add 1 cc. of 50 per cent acetic acid and 3 cc. saturated (about 30 per cent) sodium chloride. A precipitate appearing at room temperature on addition of both these reagents strongly suggests Bence-Jones protein. They state that a precipitate may also occur in urines containing globulin in amounts of 0.38 gm. per liter, but point out that such urines are uncommon. They submit the precipitate obtained, as described above, to the usual heating and cooling.

In the authors' laboratory this heating and cooling, when done in the presence of urine, has been found so unsatisfactory that the authors immediately proceeded to the further test suggested by

tested for urinary albumin and globulin. For this purpose 1 cc. of 50 per cent trichloroacetic acid in the cold is employed. In all the cases except 1, to be described below, this portion of the test has proved negative.

**Solubility of Plasma and Urinary Proteins in Bence-Jones Proteinuria.**—The authors have studied the solubility of plasma and urinary proteins in 8 patients with Bence-Jones proteinuria. (Table 77.) Seven patients had multiple myeloma, 1 of them (5, A. G.) presented an apparently solitary destructive process of less than a hen's egg size in the left humerus which had caused a pathological fracture. All other bones, particularly vertebrae and skull, were roentgenologically normal. The other patient (6, M. G.) had a diffuse amyloidosis. Extensive roentgen-ray studies of his skeleton failed to reveal any evidence of myeloma. Unfortunately no autopsy was obtained, but up to the time of death the clinical picture was clearly that of amyloidosis. The qualitative test for Bence-Jones protein as described above, was tried on the plasmas of all but No. 4 and found negative. The test was positive on all urines, and after adjustment of acidity and salt content it showed in every case complete disappearance of the precipitate at the boiling-point.

It has seemed desirable to devise a mode of study by which statements, based on the qualitative test only, could be complemented

\* If the Bence-Jones protein is very concentrated the urine must be diluted before this test is applied. In some of the material a dilution of 1 part urine to 4 parts of water was employed.

by quantitative procedures, allowing a comparison of cases observed by different investigators. The ideal procedure would be the

TABLE 77

Subject	Na <sub>2</sub> SO <sub>4</sub> molar conc	Plasma protein gm per 100 cc	Urinary proteins			Conventional plasma nomenclature
			Mg per 100 cc	Mg per 24 hrs	Unpre- cipitated protein per cent	
1 G G (37404) 7/29/26 NPN 36 mg	0.75 1.00 1.25 1.55	0.13 1.44 1.41 1.49 2.81 7.32	0 12.0 494.0 564.0 49.0 1118.0	0 95 4450 507.5 435	100.00 99.41 54.87 4.36	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
2 A B (38760) 2/14/27 NPN 44 mg	0.75 1.00 1.25 1.55	0.21 0.79 1.67 0.84 4.41 7.98	0 2.0 708.1 42.3 0 753.3	0 44 10889 6.0 0 11563	100.00 99.69 5.62 8	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
3 H H 8/20/25 NPN 40 mg	0.75 1.00 1.25 1.55	3.22 7.41 0.59 0.38 2.50 16.10	0 0 5.8 2.9 1.5 10.2	0 0 50 25 13 88	99.90 99.90 43.10 14.70	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
4 M L (56011) 3.6/31 NPN 109 mg	0.75 1.00 1.25 1.55	1.52 0.55 1.02 0.44 4.69 8.23	2.0 23.0 148.0 83.0 23.0 279.0	0 0 0 0 0 0	99.23 81.04 37.99 8.24	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
5 A G (16183) 7/1/31 NPN 50 mg and 59 mg Rehberg 27 cc	0.75 1.00 1.25 1.55	0.35 0.09 0.72 0.90 2.22 4.32	0 0 663.0 193.0 0 861.0	0 0 0 0 60 min 766	100.00 100.00 22.40 0	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
6 M G (61183) 11/2/31 Serum Ca 12.7 mg NPN 40 mg Rehberg 115 cc	0.75 1.00 1.25 1.55 1.70	0.78 0.38 0.99 1.64 0.24 3.75 7.63	0 2.0 118.0 363.8 0 483.0	0 21 1233 379.3 0 5047	100.00 99.60 75.20 0 0	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
7 C R. (61326) (a) 11/10/31 Serum Ca 13 mg Rehberg 104 cc	0.75 1.00 1.25 1.55 1.70	0.75 11.0 2.0 26.0 39.0 124.0 227.0	0 11.0 2.0 26.0 39.0 124.0 227.0	0 0 0 0 0 60 min 579	90.00 84.10 83.30 71.80 54.60	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
(b) 11/17/31 NPN 34 mg	0.75 1.00 1.25 1.55 1.70	0.54 0.47 1.59 0.66 0.24 3.47 7.01	0 26.0 42.0 139.0 121.0 335.0 863.0	0 535 889 2877 6645 6935 17864	100.00 97.00 92.10 76.00 35.80	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein
8 C H 4/6/33 NPN 47 mg Serum Ca 13.6 mg Rehberg 80 cc	0.75 1.00 1.25 1.55 1.70	8.42 4.59 2.50 0.51 0.41 1.16 17.55	0 0 306.0 236.0 26.0 568.0	0 0 0 0 0 0	100.00 100.00 46.10 4.60	Fibrinogen Globulin { Euglobulin Pseudogl I Pseudogl II Albumin Total protein

determination of the solubility curve of the purified protein as determined for serum albumin in the works of Chick and Martin and of Sørensen. With this requirement very few cases would be studied. It was hoped that, without purification of the urinary protein, the salting out with different concentrations of  $\text{Na}_2\text{SO}_4$  would give characteristic solubility curves to be compared with solubility curves of plasma proteins and of urinary proteins in other types of proteinuria. The results as represented in Figs 111 and

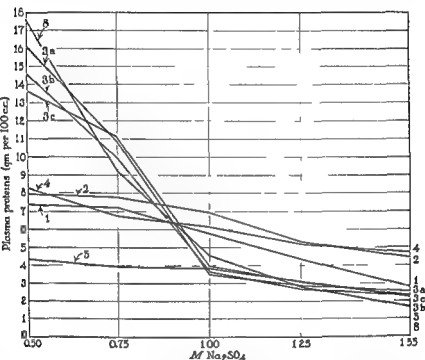


FIG. 111.—Solubility of plasma proteins in multiple myeloma. (The figures refer to patients in Table 77.)

112 are more clear cut than anticipated. Fig. 111 showing the concentration of the plasma proteins for each point of the abscissa gives the amount of protein remaining in solution at the given concentration of  $\text{Na}_2\text{SO}_4$ . Fig. 112 gives a corresponding expression of the solubility of the urinary protein but the wide variations (from 10 to 1118 mg per 100 cc) in the amount of protein rendered graphic presentation of the absolute values impracticable, the figure instead presents the percentage of urinary protein remaining unprecipitated at each  $\text{Na}_2\text{SO}_4$  concentration. In all of the samples

except 7 (C K) the Bence-Jones protein is practically completely precipitated between 1 and 1.55 molar concentration of  $\text{Na}_2\text{SO}_4$  50 per cent or more is precipitated between 1 and 1.25 molar in Case 3 in Case 5 78 per cent and in Case 2 93 per cent came down within this narrow range of concentration Chapter XXX on Proteinuria contrasts the solubility of Bence-Jones protein against anything observed in other proteinurias In regard to the sharp angles present in Fig. 112 for Case 4 at 1 molar concentration and for Cases 2 and 3 at 1.25 molar concentration the precipitations

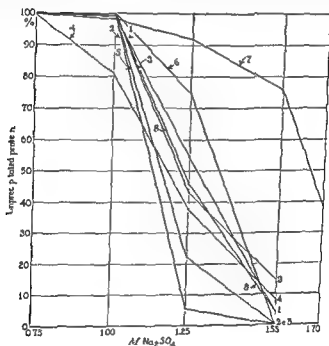


FIG. 112. Solubility of Bence-Jones proteins in the urine in multiple myeloma. (The figures refer to patients in Table 77.)

were not carried out with sufficiently small intervals between the salt concentrations to warrant any conclusions about these bends of the curves. As may be seen from Table 77 and Fig. 112 the solubility of the protein in Sample 7 shows a marked difference from that of the others, 76 per cent remaining in solution at a molar concentration of  $\text{Na}_2\text{SO}_4$  of 1.55 and 39 per cent being unprecipitated at a molar concentration of 1.7. This indicated that we were dealing here with a protein of widely different properties but definite proof was not obtained until later as described on page 538. For purification of the protein they were salted out from urine

with  $\text{Na}_2\text{SO}_4$ . In all but Case 7, a concentration of 1.55 molar  $\text{Na}_2\text{SO}_4$  produced almost quantitative precipitation. In Case 7 the urine had to be saturated with  $(\text{NH}_4)_2\text{SO}_4$  in order to salt out the protein completely. The urine was allowed to stand about a week, until the protein had settled, when the urine was syphoned off, the precipitate dissolved in water and  $\text{Na}_2\text{SO}_4$  or  $(\text{NH}_4)_2\text{SO}_4$  added to the same concentration as was employed previously. This alternate salting out and dissolving was repeated about eight times. The further purification was carried out by a method suggested by

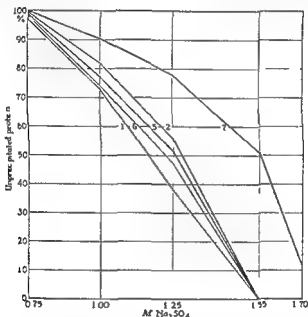


FIG. 113 — Solubility of purified Bence-Jones proteins in solutions of sodium sulphate (The figures refer to patients in Table 77.)

Dr R. A. Gortner. The pH was adjusted to the isoelectric point of the protein; the supernatant liquid was once again syphoned off and the protein transferred to cellophane tubing and dialyzed in repeated changes of water at about  $5^\circ\text{C}$  until the dialysate was sulphate-free (about one week). The cellophane sac was hung in a stream of warm dry air until the contents were reduced to a thick syrup. The syrup was then poured into a Petri dish and dried to a powder in an oven at  $40^\circ\text{C}$ . It was preserved in a refrigerator at  $0^\circ\text{C}$  and before using was dried to constant weight in a desiccator over  $\text{H}_2\text{SO}_4$ .



FIG 113 represents the salting-out curves of 4 of these samples after purification. As may be seen, Samples 1, 2, 5 and 6 present to those delineated maintains its peculiar are dealing with a protein of different constitution

In contrast to the urinary findings, the plasma proteins (Fig 111) show no precipitation beyond normal limits within the concentrations of 1 and 1.55 molar  $\text{Na}_2\text{SO}_4$ . The plasma curves when compared with the curves of the Bence-Jones protein show that of any in the

an abnormal tissue and urinary protein rather than a blood protein (Abrikossoff and Wulff and others). A pathological synthesis of plasma proteins is demonstrated in Cases 3 and 6, in whom the protein concentrations were doubled, the excess amount being

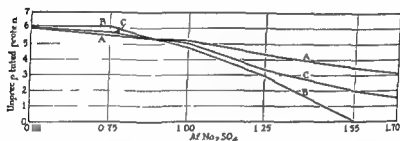


FIG 114 — Solubility of purified Bence-Jones protein in plasma. A Normal plasma. B purified Bence-Jones protein. C mixture of plasma (A) with Bence-Jones protein (B).

precipitated between 0.5 and 1 molar concentration of  $\text{Na}_2\text{SO}_4$ , viz. within the range of fibrinogen and euglobulin. No attempts at isolation and identification of this large amount of extra protein were made except that it was clearly demonstrated that it did not behave like Bence-Jones protein. In view of the unusual finding on the first case (3) the determinations were repeated twice with an interval of some days, all three determinations are reproduced

Fig 112, in spite of the difficulty in carrying out the determination upon such a small amount, shows a reasonably good agreement with the other curves. The authors have found reference to one similar case (Perlzweig, Delrue and Geschickter<sup>22</sup>).

To be assured that Bence-Jones protein in blood plasma would not be precipitated in the euglobulin group the following experi

ments, depicted in Fig 114, were performed. Curve *A* of the figure represents the solubility of plasma proteins in sodium sulphate as determined by adding 1 cc of normal plasma to ascending molar concentrations of the salt in 50-cc volumetric flasks. *B* represents the solubility of a purified Bence-Jones protein so adjusted that 25 cc had approximately the same nitrogen content as 1 cc of plasma, 25 cc were used and made up to 50 cc in solutions of sodium sulphate to correspond with those in *A*. In experiment *C*, 0.5 cc of plasma and 12.5 cc of the protein solution were employed. It may be seen that within the limits of experimental errors, the added Bence-Jones protein precipitates out within the same regions in *C* as in *B*.

It is surprising to find that in the 8 instances of Bence-Jones proteinuria in Table 77 the plasma proteins presented a most varied picture, there are represented in Fig 115 normal plasma protein masses, increase of total protein due to increased fibrinogen

plasma, slight to heavy Bence-Jones proteinuria occurred without evidence of accumulation or presence of this body in the plasma. The pseudoglobulins are the proteins least affected.

**Chemical Studies of Bence-Jones Protein**—As to the chemical and biological entity of Bence-Jones protein the situation is perhaps best elucidated by Hopkins' characterization of the protein as a uniform substance but not necessarily a chemical individual. Hopkins and Savori analyzed side by side the material from 3 patients and found a satisfactory agreement in the amino-acids which could be determined with the greatest accuracy. They therefore concluded that the materials were identical. Lüscher<sup>22</sup> working in Hopkins' laboratory concurred in this opinion. Wilson<sup>23</sup> worked on specimens from three sources, one specimen which crystallized spontaneously while the others resisted all efforts toward crystallization. On the basis of this difference and of immunological reactions studied by Bence-Jones and Wilson, Wilson holds that different Bence-Jones proteins exist. The specimen studied by Wilson which crystallized spontaneously could also be recrystallized with ease. Wilson reviews the cases in which attempts at crystallization have been successful and cites instances where investigators have interpreted crystalline deposits in microscopic sections from autopsy material as this protein. Cohen<sup>24</sup> pointed out discrepancies in various analytical and anaphylactic results, and expressed uncertainty as to whether these discrepancies depend upon differences in the material studied or upon impurities of the preparations.

A chemical study has been made in this laboratory of 6 samples

of Bence-Jones protein, from Cases 1, 2, 5, 6, 7 and 8 of Table 78 (Reported in part at the Biochemical Society, Cincinnati, April 1933) The proteins were purified as described above, and analyzed according to the nitrogen distribution method of Van Slyke<sup>22</sup> Cystine values were checked by the colorimetric method of Folin and Ciocalteu<sup>9</sup> The results of these analyses are given in Table 78 together with Luscher's analysis of Bence-Jones protein and Drummond's figures for the proteins of normal tissues It may be seen that 5 of our series are similar (Cases 1, 2, 3, 5 and 8) and in close agreement with Luscher's The fifth (Case 7) is characterized by lower ammonia-N, higher diamino-N, cystine, arginine and lysine being all increased, lower non-amino-N of the filtrate (proline and oxyproline), lower tryptophane, with tyrosine the same

TABLE 78—COMPOSITION OF BENCE-JONES PROTEINS

(In Column A are given Luscher's figures for a similar study The figures 1 2 5 6 7 and 8 refer to the number of the patient as given in Table 77 In Column B are Drummond's figures for normal tissues<sup>23</sup>)

	A	1	2	5	6	8	7	B
Amide N	9.43	9.20	9.30	9.40	9.35	9.45	5.20	5.53
Humic N	0.90	1.03	1.00	0.97	0.90	1.07	1.85	3.09
Total N of bases	23.13	22.83	23.05	22.57	22.59	22.90	30.06	30.71
Amino-N of bases	13.14	12.47	12.51	12.57	12.42	12.65	17.00	16.16
Cystine-N	1.25	1.41	1.43	1.45	1.47	1.45	2.04	0.93
Arginine-N	9.27	9.40	9.41	9.12	9.34	9.34	12.12	11.13
Histidine N	4.54	4.97	5.24	5.19	4.73	4.86	4.97	7.86
Lysine-N	8.04	7.00	6.96	7.11	7.04	7.20	10.91	9.83
Total N of filt	60.84	66.74	66.74	66.72	66.78	66.61	63.21	60.82
Amino-N of filt	61.69	62.29	62.04	62.02	61.98	61.72	59.66	55.68
Tyrosine-N		3.36	3.36	3.39	3.35	3.35	3.40	
Tryptophane-N	2.44	1.60	2.12	2.03	1.97	1.07	1.01	
Non-amino-N of filt	5.15	4.45	4.66	4.70	4.80	4.59	3.65	4.94
Total N per cent protein		16.20	16.22	16.20	16.24	16.21	16.22	
Ash per cent pro- tein		0.19	0.16	0.16	0.20	0.20	0.19	
Total N	100.28	99.85	100.12	100.37	99.61	100.03	100.3	100.40

\* Drummond Biochem J 10 473 1916

The molecular weight of the Bence-Jones protein is in two different parts, the heavy part being about half that of serum albumin, the minimal weight as 12,250 or twice this 24,500, the latter figure being about one-half that of the minimal molecular weight they have given for serum albumin (45,000, and about one-third of the minimal molecular weight for serum globulin (80,000) Their calculation for Bence-Jones protein was made on the basis of Folin

and Looney's<sup>21</sup> tryptophane determinations and Hopkins and Savory's sulphur analysis. It may be noted that they omitted in their calculations any consideration of the histidine content since this would lead to a molecular weight of 73,500, a figure that they considered too high. Svedberg<sup>22</sup> using the ultracentrifuge, placed the molecular weight at  $35,000 \pm 1000$ , a figure approximately one half of his estimate for serum albumin (67,500) and one third that for serum globulin (103,800).

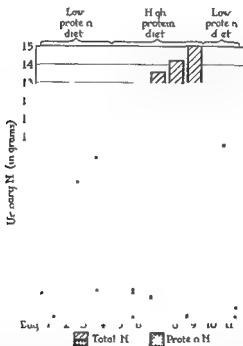


FIG. 115—Metabolism experiment. Case 5 (C.H.) on low, high and low protein intake. The output of Bence-Jones protein is approximately constant.

The classification of Bence-Jones protein, once a subject of lively discussion, calls for detailed consideration no more its character as a protein being agreed upon and its similarity and dissimilarity to the globulins having been repeatedly discussed. The same might be said about the relation between protein intake and amount of Bence-Jones body lost in the urine. Magnus-Levy, in prolonged metabolism experiments, demonstrated a slight positive correlation between nitrogen intake and Bence-Jones excretion, and believes there is an exogenous as well as an endogenous factor

in Bence-Jones proteinuria. The conclusion reached by Allard

cases extensively studied (Cases 1 and 8) the same seemed to be true. Fig 115 represents a metabolism experiment on the latter. On account of his extreme illness the experiment could not be prolonged.

### CLINICAL PATHOLOGICAL CONSIDERATIONS OF BENCE-JONES PROTEINURIA \*

Special interest has been bestowed upon Bence-Jones proteinuria because of the high incidence of chronic kidney disease in patients suffering from multiple myeloma (Wallgren<sup>44</sup> Geschickter and Copeland<sup>45</sup>). Supporters (Th Fahr, Lichtwitz) of Epstein's theory of nephrosis as due to altered plasma protein by its leakage damaging the kidney have seen in Bence-Jones proteinuria an analogy to the nephrosis. Though the kidney lesions found in multiple myeloma might vary, some instances have been classified as contracted nephrotic kidneys as conceived by Th Fahr (Thannhauser and Krauss<sup>46</sup>). In this connection reference has also been made to Longcope's work on the effects of foreign protein on the kidney in man. Without denying the possible correctness fully or in part of this view of the relation between damaged kidneys and Bence-Jones proteinuria certain difficulties in its acceptance shall be discussed and another line pointed out for the investigation of the kidney involvement in multiple myeloma.

The only convincing evidence of the presence of detectable amounts of Bence-Jones protein in the circulating blood was presented by Abderhalden<sup>1</sup> and by Wilson<sup>48</sup>. Other investigators: e. g. Jacobson<sup>49</sup> Perlzweig, Delrue and Geschickter<sup>50</sup> Taylor, Miller and Sweet<sup>41</sup> Magnus Levy<sup>51</sup> Hewitt<sup>52, 53</sup> and Munzer<sup>54</sup> have reported isolation of traces of a protein which possessed Bence-Jones like properties. In view of the fact that many of these plasmas contain abnormally large amounts of euglobulin thereby imparting properties to the plasma quite different from those of normal plasma it is believed that isolation of a compound with aberrant solubilities

\* About 7000 mg of total serum protein

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\* With Hilding Berglund

In 3 of the authors' cases unsuccessful attempts were made to demonstrate the protein in the blood

Turning to the situation in the urine it is important that Hopkins and Savory in their 3 cases and Colin and Dennis in their case found no protein other than the Bence-Jones present in the urines they studied. The authors have no evidence in their 8 cases of the presence of any proteins other than the Bence-Jones. Thannhauser and Krauss<sup>40</sup> feel convinced that in their case a slight amount of serum proteins was present besides the Bence-Jones. The only case among the authors' records in which albumin was admixed with the Bence-Jones protein in the urine was one brought to their attention by Dr. E. T. Bell who sent a sample of urine obtained postmortem. It contained large amounts of protein which was about 80 per cent Bence-Jones protein and about 20 per cent albumin. The patient died of kidney disease. His serum protein was

does not offer strong evidence of any etiological relation between the two. I shall further be interested to know of the patient who during four years excreted 146 kilos of Bence-Jones protein daily. When after this period of time autopsy was obtained,

than serum albumin easily escapes through the glomeruli showing little or no accumulation in the blood. In finding its way into the urine it leaves the glomeruli unharmed without causing any alteration in the permeability of the finer glomerular structure as evidenced by the frequent absence of detectable traces of serum albumin in the urine. After at least 146 kilos of Bence-Jones protein had been filtered through the glomeruli (Hopkins and Savory, Case A) the kidneys still appeared normal and even in markedly contracted kidneys in myeloma the glomeruli on ordinary microscopic examination may show few scattered pathological changes only (Thannhauser and Krauss<sup>40</sup>). The Bence-Jones protein once having passed through the wall of the glomerular tuft should endanger the kidney no more no one as far as the authors are aware postulating any tubular reabsorption of protein.

In rare instances abundant crystallization of protein has been

observed in the lumina of the tubules. In 1 case of multiple myeloma (Lohlein<sup>22</sup>) Bence-Jones proteinuria was observed during life no other protein being present in the urine. In 2 other cases Koch<sup>19</sup> and Rehsteiner<sup>23</sup> stated that no reason to assume Bence-Jones proteinuria existed. Ordinary albuminuria was present. Glomerular changes as in glomerulonephritis were absent in all 3 cases. The diagnoses of nephrosis were made. It is important to note that the crystals were found in the tubular lumina only the interstitial tissue being free. Binding evidence that they were formed during life and not immediately before or after death was present in all cases in the form of foreign body giant cells attacking the crystals in the lumina. Kleme<sup>20</sup> has added another observation less clear cut than Lohlein's of crystalloid protein casts surrounded by giant cells in the renal tubules in a case of multiple myeloma with Bence-Jones proteinuria.

The intratubular crystallization of protein is of interest in connection with Wilson's case of spontaneous crystallization in the

(Abrikossoff and Wulff<sup>2</sup>)

The high positive correlation of multiple myeloma and chronic renal disease requires a pathogenetic consideration if possible based on a characteristic metabolic disturbance other than the proteinuria. The creatinuria common in myeloma in this connection deserves no consideration. The course in general pathology in many universities no doubt includes microscopic kidney slides from cases of myeloma for the demonstration of calcium metastases as first described by Virchow in osteomalacia and later in other conditions with extensive decalcification of the skeleton.

About the mechanism by which calcium is eliminated through the kidney knowledge is wanting. The authors had 1 case of multiple myeloma with most extensive decalcification like severe osteomalacia in which multiple spontaneous fractures were present. The patient died before complete studies were made. The following data are available. The urine showed a definite trace to a heavy cloud of albumin no Bence-Jones protein was found repeated attempts to demonstrate it were unsuccessful. On admission the urine showed a nephritic sediment. Toward the end there was hypostenuria. The blood calcium on three different blood samples was 17 mg, 16.9 mg and 20 mg per 100 cc serum. Another myeloma patient with normal urine but with extensive decalcification presented a serum calcium of 12.2 mg. The Rehberg test revealed a filtration rate of 63 cc per minute only. (The plasma creatinine after the creatinine ingestion was 10.2 mg the concentration ratio was 66.) Here therefore we have an instance of

definitely reduced filtration rate without albuminuria. An even more marked instance is Case 5. This patient in two Rehberg tests two weeks apart had a filtration rate of 27 and 28 cc only. (The corresponding plasma creatinine values were 9.9 mg both times and the concentration ratios 25 and 22). Case 7 had a serum calcium of 18.6 with a creatinine clearance of 32 cc per minute while another patient not otherwise discussed in this chapter had a serum calcium of 18.7 at the time his creatinine clearance was 20 cc per minute.

These unquestionably severely damaged kidneys did not let through any plasma proteins as shown both by qualitative tests and by Fig. 112 though in most of these cases Bence-Jones protein was eliminated in abundance. Whatever may be the causative agent of the renal lesion in myeloma the process is expected pathogenetically to differ from the ordinary chronic glomerulonephritis with its primary glomerular damage and its albuminuria.

Though elevated blood calcium is not a constant finding in metastases instance Paul they are not to be confused with the extensive calcifications with different localization

new chapter on pathology opened by Pfannenstiel in 1927<sup>13</sup> still is largely unwritten it appears that the various pathological changes among which characteristic renal lesions constitute one can be explained on the basis of an altered and intensified calcium metabolism. An extreme hypercalcemia occurs in the dog (Demole and Fromherz<sup>14</sup>) a change absent or less marked in the rabbit (Harris and Stewart<sup>15</sup>). In all experimental animals the kidneys show marked changes the primary basis for which are calcium deposits within the tubules in the interstitial tissue and also though less marked in the glomerular capsular space (Kreitman and Hinzelmann<sup>16</sup> and Schmidtman<sup>17</sup>). It is worth noting that the changes so far described have been the results of experiments of short duration.

Bell<sup>18</sup> in an extensive study of the pathology of the recorded cases as well as of his own series concludes that the renal injury in multiple myeloma is due to obstruction of the tubules by casts. Numerous other observers have recorded the presence of large numbers of casts in the tubules. It is not certain however whether the casts are the cause of the tubular degeneration or the effect



Bell implies the former interpretation and states that in his own series no casts were found in 2 cases (Cases 80 and 81) in which no Bence-Jones protein was excreted. His Case 81 however is the same as the authors J B who showed a definitely lowered creatinine clearance (63 cc per minute), and demonstrates that the kidney injury may be independent of Bence-Jones proteinuria and casts.

More recently, an even more striking case bearing upon the subject has been observed by one of the authors (Medes). The patient (Lankenau Hospital 107-34) was admitted about two months before death. At that time only a very faint trace of albumin was found in his urine although his creatinine clearance test was reported as 5.5, his serum calcium 17 and his blood urea nitrogen 144 mg per 100 cc. At necropsy a widespread myeloma was demonstrated. The kidneys resembled those of the patient described by Perla and Hutner.<sup>11</sup> The glomeruli were largely normal with some thickening and hyalinization of the basement membranes. The tubules were markedly atrophic. Large numbers of casts were present in which a considerable amount of calcium was demonstrated. Calcium was also found in the walls of the tubules themselves. No Bence-Jones protein was present in his urine.

In view of these findings in experimental hypercalcemias and in multiple myeloma where the decalcification has been going on for years and sometimes reaches extreme degrees consideration should be given to the correlation of the frequently present renal disease with the increased calcium elimination rather than with the Bence Jones proteinuria.

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## CHAPTER XXII

### SALTS AND EDEMA \*

By A BAIRD HASTINGS PH D

**Introduction**—It is commonplace today to state that the problem of edema is intimately related to the problem of physiological regulation. McLean<sup>1</sup> has made clear the importance of such a conception in his discussion of edema as a problem of volume regulation within the organism. In viewing the problem as a whole it is not sufficient, as he pointed out, to consider simply the physico-chemical influences involved; the role of the nervous and chemical regulatory factors must be considered as well. The application of the formulation known as the Gibbs-Donnan equilibrium, which describes equilibrium conditions between phases separated by preferentially permeable membranes, can be of little aid in indicating causal factors of edema. As in the case of all thermodynamic concepts, this formulation is a statement of equilibrium states and gives no clue as to the path taken in reaching these states.

This does not mean, however, that insofar as movements of electrolytes and water are influenced by ions incapable of passing limiting barriers, changes toward the equilibrium states indicated by the Donnan formulation do not occur. On the contrary, any discussion of the relation of salts to edema must include an account of these influences, and an estimate of their magnitude would be desirable.

Without attempting to account for the physiological influences operating in the regulation of rates of absorption and excretion, this chapter will be an effort to discuss the problem. *Given conditions in which there is salt accumulation in the organism, or a change in reaction within the organism, or both: to what extent, if any, does our present knowledge of the movements of electrolytes and water account for the physiological effects observed?*

At the outset it should be stated that the time is not yet ripe for an adequate discussion of even this restricted section of the problem of edema. However, some data are now available and it may prove useful to attempt to apply them in an endeavor to point out where some of the gaps in our knowledge of electrolyte and water balance occur.

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## FACTS CONCERNING SALTS AND EDEMA

Investigators in many countries have made experiments and clinical observations on the relation of salts to edema. Among the names prominent in these studies are Magnus<sup>11</sup> Wahlgren<sup>23</sup> Magnus Levy<sup>16</sup> Wertheimer<sup>24</sup> Mond<sup>25</sup> Baird and Haldane<sup>2</sup> and Blum.<sup>4</sup> Some have attempted to assign a causal relationship between salt retention and edema formation; others have fixed their attention on the changes in acidity of the cells and their environment; still others have looked to the change in balance between the osmotic and hydrostatic pressure factors for the clue to edema formation and control.

A point which is an obvious corollary to the above considerations is that edema fluid can be formed only to the extent that salts and water are available for its formation. The concentrations of the inorganic salts of edema fluids are with only slight differences practically equal to those of an ultrafiltrate of blood plasma. It may be anticipated therefore that unless an adequate supply of certain salts is available edema fluid cannot be formed. Since sodium chloride is quantitatively by far the most important inorganic constituent of body fluids, it in turn becomes quantitatively the most important salt favoring the formation of edema.

Man normally ingests and excretes approximately 3 to 6 gm of sodium chloride and 1 to 2 liters of water a day. These amounts may be widely varied without the formation of edema. And yet if the amount of salt ingested exceeds the amount which can be eliminated, edema can be demonstrated even in the normal individual. For example, Baird and Haldane observed edema in a normal individual following the ingestion of 40 gm of sodium chloride. In conditions where a so-called tendency to edema is present, the ingestion of much smaller amounts of salt is adequate for the development of edema. On the other hand, withholding salt and water in cases with a tendency to edema often serves to prevent its formation, or if present, to provide for its elimination. In other words, by denying the organism the two most essential constituents of edema fluid, the formation of edema can in many instances be prevented.

Of course, it is never so simple as this in the actual clinical case. A constant flow of fluids is an essential element of the life of cells, and even if salts are withheld almost entirely, the wasting of tissues provides a source of salts which can hardly be obviated.

One may cite certain exaggerated experimental conditions which illustrate the role that the magnitude of available salt and water play in the development of edema. For example, it has been experimentally demonstrated by Ivy and his associates<sup>3</sup> that a nephrectomized dog will develop edema if salt and water are sup-

plied in sufficient quantity. This apparently never happens in normal dogs in spite of forcing salt and water by mouth.

A most complete and accurate study of the metabolism of various salts by a normal subject and a subject with nephrotic edema has been carried out by Loeb, Atchley, Richards, Benedict and Driscoll.<sup>1</sup> Their results may be summarized as follows:

1 Sodium chloride when given by mouth was retained to some extent by both subjects however the retention was greater in the nephrotic patient than in the normal individual

2 Potassium chloride when administered behaved like a mildly acid salt. More chloride was absorbed from the intestine than potassium and potassium was excreted faster than chloride. Only a slight retention of this salt occurred, however.

3 When  $\text{NH}_4\text{Cl}$  was given the usual acidosis following administration of this salt resulted but no diuresis was observed

Throughout the study the normal subject and the nephrotic

94

### Summary

It should also be mentioned that the ingestion of sodium bicarbonate causes a retention of sodium and water. Whether or not this is a result of the alkalosis produced or of the sodium ion is still a matter of discussion.

The clinical observation that alkali salts such as sodium bicarbonate tend usually to increase edema and acid forming salts such as ammonium chloride and calcium chloride will often decrease edema led to a study of the water balance in patients with edema following congestive heart failure. This work was carried out

by  
Coll

of from four to eight days.

It was found that although for the first day or so after giving sodium bicarbonate there was retention of water and an increase in edema this was not always maintained in spite of the continued administration of sodium bicarbonate. The reverse occurred after giving ammonium chloride. That is on the first day after the administration of ammonium chloride was begun there was an excessive loss of water. Subsequently the loss of water above the intake was slight or within experimental error. A brief period of increased excretion of water followed the cessation of the administration of sodium bicarbonate and increased retention of water

followed cessation of the administration of ammonium chloride. These observations might be interpreted as providing direct quantitative proof that alkalosis favored water retention, and acidosis, water excretion.

formation or present a new one. Rather, an attempt will be made

this subject its objective will be attained

### THE ELEMENTS OF THE SYSTEM

At the risk of simplifying the situation more than is legitimate, the biological system will be regarded as consisting of the following quantitatively important phases: namely, the cellular elements of the blood, the blood plasma, the extracellular fluids and the cells of the tissues. It would be idle to attempt a quantitative differentiation of the relative importance of the different tissues at this time. Suffice it to say that the muscles and subcutaneous tissues are presumably those of greatest quantitative importance in effecting changes in water balance.

The blood cells and plasma may be conceived as separated by a

through this membrane is also probably true. The functional nature of the barrier between the tissue cells and the extracellular fluid is by no means clearly understood. This is one of the fields in which more experimental data are needed. It may be assumed, however, that normally these membranes are also impermeable to proteins and cations. By analogy with blood, it might be supposed that cell membranes are permeable to  $H^+$ ,  $Cl^-$ ,  $HCO_3^-$  and other small anions. This is not the case, however, as will be subsequently pointed out. Separating the blood stream and the extravascular

There exists in the capillaries a mean hydrostatic pressure of a determined magnitude, and there is within the tissues a mechanical pressure of uncertain magnitude. Such a simplified scheme as this is concerned solely with the thermodynamic factors of pressure

and ionic activity, and in no way minimizes the importance of such physiological factors as nervous and hormonal control, or rates of absorption and excretion.

**The System, Erythrocytes Plasma**—The system, erythrocytes-

physico-chemical system has been made by Van Slyke and Henderson and their collaborators<sup>6,22</sup>. As a result of their work the quantitatively important factors concerned with electrolyte and water distribution between plasma and erythrocytes have been found and related\*. The major changes occurring in electrolyte and water distribution when the oxygen and  $\text{CO}_2$  tensions of the blood are altered have been satisfactorily accounted for by taking into account the fact that the erythrocytes behave as if provided with a membrane impermeable to bases and proteins and by postulating that at equilibrium there will exist (a) equality of equivalents of positive and negative ions (b) osmotic equilibrium (c) distribution of diffusible ions satisfying the Gibbs-Donnan distribution law.

Briefly these facts are as follows. (a) In normal arterial blood at pH, 7.4 there exists an unequal distribution of bicarbonate, chloride and hydrogen ions between plasma and erythrocytes. Experiment has shown that the distribution may be expressed approximately by the ratios

$$\frac{[\text{HCO}_3^-]_c}{[\text{HCO}_3^-]_p} = 0.77 \quad \frac{[\text{Cl}^-]_c}{[\text{Cl}^-]_p} = 0.61 \quad \frac{[\text{H}^+]_c}{[\text{H}^+]_p} = 0.5$$

(b) The addition of carbon dioxide to blood has long been known to increase the bicarbonate concentration of both plasma and cells though the latter increases more than the former. Furthermore the chloride concentration of the cells increases at the expense of the chloride concentration of the plasma. These changes are net

1

both the plasma and cells is lowered.

2 At low pH there is less base bound by the proteins—in this case oxyhemoglobin. This base though not capable of diffusing into the plasma is free to combine with chloride and bicarbonate ions which pass into the cells from the plasma.

3 There is a redistribution of diffusible ions until the Gibbs-Donnan equilibrium is again established.

4 Water passes from the plasma into the erythrocytes until osmotic equilibrium is restored.

\* The experimental work of these investigators was done on the system, erythrocytes-serum but there is reason to believe that the same relations hold for the system erythrocytes-plasma which is the physiological system discussed here.



An additional experimental fact which further substantiates the above explanation is that oxygenation and reduction of blood at constant pH change the distribution of chloride bicarbonate and hydrogen ions in a similarly predictable manner.

This brief summary of the effect produced by alteration in the reaction and degree of oxygenation of the blood has been introduced to illustrate how the distribution of water between serum and cells depends in part on non-diffusible protein ions.

**The System Plasma Extracellular Fluid**—The situation in the system plasma-extracellular fluid requires more study than has yet been accorded it. However several groups of investigators have made careful quantitative observations which may be mentioned. Loeb, Atchley and Palmer<sup>11</sup> have studied the system serum-edema fluid. Hastings, Sillesen, Sendroy and Van Slyke<sup>7</sup> studied this system and other serum transudate systems both natural and artificial. Pincus and Kramer<sup>1</sup> have studied ionic distribution between serum and cerebrospinal fluid. Duke-Elder<sup>2</sup> has compared the concentrations of certain constituents of the aqueous and vitreous humors and blood serum. Arnold and Mendel have made a comparison of the constituents of thoracic lymph and serum.

From the earlier experiments it seemed that the unequal distribution of inorganic ions could be accounted for by assuming that the capillary wall was freely permeable to crystalloids and not to

hydrogen ions may be satisfactorily accounted for on the original hypothesis that the capillary wall is permeable to plasma

distribution of ions which leads to a distribution ratio of  $\frac{(A)_s}{(A)_f} = 0.96$  where  $(A)_s$  stands for concentration of diffusible anions in the serum and  $(A)_f$  the concentration in the protein free fluid. The ionic distribution ratios found in Van Slyke's laboratory were

$$\frac{(\text{HCO})_s}{(\text{HCO})_f} = 0.96 \quad \frac{(\text{Cl})_s}{(\text{Cl})_f} = 0.97 \quad \frac{(\text{Na})_s}{(\text{Na})_f} = 0.91 \quad \frac{(\text{H}^+)_s}{(\text{H}^+)_f} = 0.91$$

Potassium and calcium seem not to be distributed according to this simple hypothesis. Whether this is due to permeability effects and calcium compounds in

to study the effect of alterations in pH on the system plasma-extracellular fluid.

From the plasma protein concentration and from the unequal distribution of ions between plasma and extracellular fluid Van Slyke has calculated that at normal pH and normal protein concentration the plasma will have an osmotic pressure of 25 mm of mercury in excess of that of the extracellular fluid. Approximately four-fifths of this difference in osmotic pressure, or 20 mm Hg is due to the plasma proteins and one-fifth or 5 mm Hg is due to the Donnan equilibrium effect. This means that at equilibrium a mean hydrostatic pressure of approximately 25 mm must exist in the blood stream to balance the osmotic pressure of the plasma.

per liter are equal it is apparent that twice as much of the osmotic pressure of the plasma proteins is attributable to albumin as to globulin. Therefore the reduction in plasma albumin which occurs clinically has a relatively greater effect in reducing the colloidal osmotic pressure of the plasma than the simple reduction in total protein concentration expressed as grams per liter would indicate. It should also be noted that the difference in osmotic pressure between plasma and extracellular fluid due to the existing Gibbs-Donnan equilibrium is of a relatively small order of magnitude and it is only this fraction of the plasma osmotic pressure which would be particularly sensitive to changes in ionic environment. This matter has been well discussed by Ishberg<sup>4</sup> in a consideration of the relation of the serum proteins and lipoids to osmotic pressure. The importance of plasma proteins in edema formation has been clearly proven by Lister<sup>5</sup> and by Barker<sup>6</sup> by the production of

from blood plasma into tissue spaces and back into the blood stream is given in Fig. 116. This diagram has with certain changes been drawn after that published by Schick and Clausen as modified by Peters and Van Slyke.<sup>70</sup>

The first diagram illustrates the normal situation. The hydrostatic pressure of the blood is indicated as falling in the capillaries from about 40 mm Hg to 0. (The fall is probably not linear with distance.) The colloidal osmotic pressure of the plasma is shown rising slightly as the blood traverses the capillaries. The result of these forces operating in opposite directions is the filtration of fluid, which occurs rapidly at first and then more slowly as the forces tend to become equal finally when the osmotic pressure exceeds the hydrostatic pressure the fluid is reabsorbed into the blood stream. (In this description no attempt has been made to allow

An additional experimental fact which further substantiates the above explanation is that oxygenation and reduction of blood at constant pH change the distribution of chloride bicarbonate and hydrogen ions in a similarly predictable manner.

This brief summary of the effect produced by alteration in the reaction and degree of oxygenation of the blood has been introduced to illustrate how the distribution of water between serum and cells depends in part on non-diffusible protein ions.

**The System Plasma Extracellular Fluid**—The situation in the system plasma-extracellular fluid requires more study than has yet been accorded it. However several groups of investigators have made careful quantitative observations which may be mentioned. Loeb, Atchley and Palmer<sup>12</sup> have studied the system serum-edema fluid. Hastings, Salvesen, Sendroy and Van Slyke<sup>7</sup> studied this system and other serum transudate systems both natural and artificial. Pincus and Kramer<sup>1</sup> have studied ionic distribution between serum and cerebrospinal fluid. Duke-Elder<sup>6</sup> has compared the concentrations of certain constituents of the aqueous and vitreous humors and blood serum. Arnold and Mendel<sup>13</sup> have made a

capillary wall was freely permeable to crystalline and not to substances of colloidal dimensions but more recent work seems to throw some doubt on this simple explanation. However as a first approximation the distribution of chloride bicarbonate sodium and hydrogen ions may be satisfactorily accounted for on the original assumption that the capillary wall is normally impermeable to plasma albumin and globulin. Further these proteins acting as anions on the alkaline side of their isoelectric point serve to establish an unequal distribution of ions which leads to a distribution ratio of  $\frac{(A)_s}{(A)_f} = 0.96$  where  $(A)_s$  stands for concentration of diffusible anions in the serum and  $(A)_f$  the concentration in the protein free fluid. The ionic distribution ratios found in Van Slyke's laboratory were

$$\frac{(\text{HCO}_3)_s}{(\text{HCO}_3)_f} = 0.96 \quad \frac{(\text{Cl})_s}{(\text{Cl})_f} = 0.97 \quad \frac{(\text{Na})_f}{(\text{Na})_s} = 0.94 \quad \frac{(\text{H}^+)_f}{(\text{H}^+)_s} = 0.91$$

Potassium and calcium seem not to be distributed according to this simple hypothesis. Whether this is due to permeability effects or the presence of complex potassium and calcium compounds in serum is not as yet known. That a portion of the serum calcium is combined with proteins is known. From the determinations now available on the base bound by serum proteins it should be possible to study the effect of alterations in pH on the system plasma-extracellular fluid.

From the plasma protein concentration and from the unequal distribution of ions between plasma and extracellular fluid, Van Slyke has calculated that at normal pH and normal protein concentration the plasma will have an osmotic pressure of 25 mm of mercury in excess of that of the extracellular fluid. Approximately four fifths of this difference in osmotic pressure, or 20 mm Hg is due to the plasma proteins and one-fifth or 5 mm Hg is due to the Donnan equilibrium effect. This means that at equilibrium a mean hydrostatic pressure of approximately 25 mm must exist in the blood stream to balance the osmotic pressure of the plasma.

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per liter are equal it is apparent that twice as much of the osmotic pressure of the plasma proteins is attributable to albumin as to globulin. Therefore the reduction in plasma albumin which occurs clinically has a relatively greater effect in reducing the colloidal osmotic pressure of the plasma than the simple reduction in total protein concentration expressed as grams per liter would indicate. It should also be noted that the difference in osmotic pressure between plasma and extracellular fluid is of a magnitude such that it is only this fraction of the total osmotic pressure

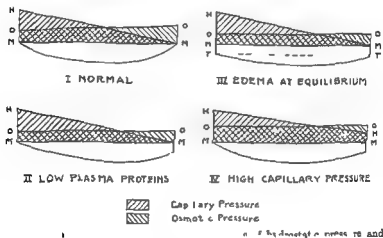
and it is only this fraction of the total osmotic pressure which would be particularly sensitive to changes in ionic environment. This matter has been well discussed by Fishberg<sup>4</sup> in a consideration of the relation of the serum proteins and lipoids to osmotic pressure. The importance of plasma proteins in edema formation has been clearly proven by Leiter<sup>5</sup> and by Barker<sup>6</sup> by the production of experimental edema in dogs following plasmapheresis.

**Pressure Forces and Movement of Fluid.** A diagrammatic representation of the forces which provide for the movement of fluid from blood plasma into tissue spaces and back into the blood stream is given in Fig. 116. This diagram has with certain changes been drawn after that published by Schade and Clausen as modified by Peters and Van Slyke.<sup>20</sup>

The first diagram illustrates the normal situation. The hydrostatic pressure of the blood is indicated as falling in the capillary from about 40 mm Hg to 0. (The fall is probably not linear with distance.) The colloidal osmotic pressure of the plasma is shown rising slightly as the blood traverses the capillary. The result of these forces operating in opposite directions is the filtration of fluid, which occurs rapidly at first and then more slowly as the forces tend to become equal finally when the osmotic pressure exceeds the hydrostatic pressure the fluid is reabsorbed into the blood stream. (In this description no attempt has been made to allow

for the amount of fluid which finds its way back into the circulation by way of the lymph channels)

The second diagram illustrates the situation when the net colloidal osmotic pressure of the plasma is lowered below normal. This may be the result either of a lowered plasma protein concentration or of an altered permeability of the capillary membrane, so that some protein passes through it. The hydrostatic pressure is here illustrated as remaining normal. As a result of these unbalanced forces of filtration and reabsorption an excess of fluid will be left in the interstitial spaces, after the blood has traversed the capillary, which will continue to accumulate until equilibrium is again established.



from the plasma at various positions along the capillary

Such an equilibrium is illustrated in the third diagram. The hydrostatic pressure and the colloidal osmotic pressure are those of the second diagram. In addition the existence of a hydrostatic pressure of the fluid within the interstitial spaces by the area  $M-M-T$  has been indicated. This will provide a back pressure which will be added to the osmotic pressure of the plasma proteins. The forces will be the filtration of some and the absorption of an equal amount. This will be considered to be in a state of equilibrium until some change occurs in the forces which will provide for its increase or its reabsorption.

Such a change might conceivably be brought about by 1 An increase in the net colloidal osmotic pressure of the plasma

2 A decrease in the hydrostatic pressure of the blood in the capillaries

3 An increase in the back tissue pressure

Presumably the first named is the change which usually takes place but since it does not always occur clinically with the elimination of edema the other possibilities should be considered

Finally in the fourth diagram there is illustrated the usually accepted mechanism of the formation of cardiac edema The hydro-

plasma is represented as normal The net result of this disturbance of forces would be to provide for an excess of fluid filtered over that reabsorbed

These then are the primary forces conceivably operating in the formation of edema Furthermore since they are the forces normally operating in fluid exchange changes in their magnitude alone would account for most of the abnormalities observed

#### EFFECT OF CHANGING pH IN VIVO ON THE ELECTROLYTE-WATER EQUILIBRIUM

The experiments on the blood previously referred to on the effect of changing the pH of the system erythrocytes plasma were limited to *in vitro* experiments It was of interest to know whether the conclusions reached concerning electrolyte and water distribution by experiments *in vitro* are equally applicable to conditions *in vivo* To determine this H N Harkins and the author have performed a series of experiments on the electrolyte and water distribution in

found in these experiments that the distribution ratio of chloride

by its action on the blood and since it was found not to be excreted in the course of the experiments it was supposed that similar adjustments took place between the tissue cells and the extracellular fluid

Experiments have also been performed in which experimental alkalosis was produced in animals by sodium carbonate These

experiments led to changes of an opposite nature. The distribution ratios of chloride and bicarbonate between erythrocytes and plasma were decreased instead of increased. There was correspondingly a passage of water from erythrocytes to the plasma. Since tissue analyses were not made we have no knowledge of the effect which the alkalosis had outside of the blood stream. There was of course in these experiments a marked diuresis.

### ELECTROLYTE AND WATER DISTRIBUTION FOLLOWING THE ADDITION OF NaCl TO BLOOD IN VITRO

If the conclusions reached by Van Slyke, Wu and McLean concerning the distribution of electrolytes between erythrocytes and plasma be possible, the addition of NaCl in isotonic aqueous solution and (2) making plasma hypertonic with NaCl alone. Experiments to test whether the predicted changes are actually realized have been performed by Morgan<sup>18</sup> in L. J. Henderson's laboratory and by Van Dyke and the author.

1. The addition of NaCl in isotonic solution caused an increase in chloride and a decrease in  $\text{HCO}_3$  concentration within the serum phase. If the pH of the serum was kept constant however there was a redistribution of the chloride and bicarbonate ions until

condition the magnitude of the plasma phase may be increased without a change of significant magnitude in the water or electrolyte distribution.

2. Making serum hypertonic with NaCl did however influence the electrolyte and water distribution. There was an increase in

making the plasma hypertonic caused a lower distribution ratio of chloride and bicarbonate between erythrocytes and plasma. There also occurred a passage of water to the plasma to restore osmotic equilibrium.

### CHARACTERISTICS OF THE SYSTEM TISSUE-EXTRACELLULAR FLUID

From a physico-chemical standpoint the most important difference between the systems, tissue fluid and erythrocytes plasma is that of the permeability of the membranes separating the phases. Both blood and tissue cells are impermeable to cations and proteins.

but whereas the former are freely permeable to chloride the latter (or at least those of striated muscle) are apparently impermeable to this ion. Peters<sup>19</sup> has pointed out that such a conclusion is compatible with certain available knowledge concerning this system and we have reached a similar conclusion from data obtained by L. Eichelberger and the author. For example muscle removed from the normal living organism was found to have a chloride concentration of only 20 millimols per kg. of tissue even on a water basis this amounted to only 28 millimols per kg. of water. The chloride concentration of blood plasma lymph and edema fluid amounts to approximately 100 millimols per kg. of water. If one assumes that 20 per cent of the bulk of muscle analyzed is extracellular fluid whose composition corresponds to that of edema fluid all of the chloride found in the muscle is accounted for. Similarly, in the case of sodium muscle was found to have 31 millimols per kg. of tissue whereas edema fluid had 145 millimols per kg. If one assumes that 21 per cent of the muscle is extracellular fluid all of the sodium is thereby accounted for. The muscle cells contain also approximately 100 millimols per kg. of water—largely potassium—to which the cells are normally impermeable.

When muscle is removed from an animal and equilibrated *in vitro* with the serum of the same animal under the most favorable conditions of pH and temperature the permeability relationships change radically. When equilibrium is established it is found that the chloride concentration has risen from 28 to 72 millimols per kg. of water. Under these conditions a change in pH causes a shift in the chloride distribution between muscle and serum in a direc-

*in vitro* and *in vivo*

tem erythrocytes plasma

## EFFECT OF pH ON THE SYSTEM MUSCLE-EXTRACELLULAR FLUID

In order to test whether the Gibbs-Donnan distribution law accounted for the changes produced in the system muscle-extracellular fluid when the reaction and salt content of the organism were altered the following experiments were performed.

Specimens of muscle from anesthetized dogs were removed from



one side of the animal and blood was drawn simultaneously. A carbon dioxide acidosis was then produced in the animals by causing them to rebreathe in a closed system until the blood pH fell to between 7.0 and 7.1. Muscle from the other side and blood were then again removed for analysis of their sodium chloride and water concentrations. It was found that both the sodium and chloride decreased by comparable amounts. This could be satisfactorily accounted for by the assumption that there had been a decrease of between 15 and 20 cc of extracellular fluid per kg of muscle. Such a result could hardly be the consequence of the Gibbs Donnan equilibrium law but rather the intervention of physiological processes. It is of interest however to point out in this connection that these experiments constitute direct evidence for the generally recognized observation that acidosis tends to diminish edema.

The experiments just cited are concerned with the effect of pH changes on the distribution of water and salts in the organism without the addition of material capable of being used for edema fluid. Furthermore if the above interpretations of our experimental results are correct an analytical method of estimating quantitatively the extent of edema is suggested namely that by sodium and chloride analyses of tissue impermeable to these ions an estimate of the amount of extracellular fluid per kilogram of tissue may be made.

From the foregoing it may be seen that the direct application of the Gibbs Donnan distribution law does not account for the changes in water and salts in the system muscle-extracellular fluid as affected by pH. However the following considerations should not be overlooked. When the pH of the plasma is lowered by carbon dioxide there is as we have stated a lower pH within the red cells and subsequent movement of chlorides and water into the cells. This results in slightly raising the colloidal osmotic pressure of the plasma which in turn would tend to draw fluid from the extracellular space until equilibrium was again restored. Whether this is a quantitatively important factor cannot be definitely stated at present.

#### EFFECT OF NaCl ON THE SYSTEM MUSCLE-EXTRACELLULAR FLUID

When 1 liter of isotonic NaCl solution was injected intravenously instead of changing the pH it was found that the estimated *in vivo* in extracellular fluid of muscle was approximately 20 cc per kg. This provides direct evidence that when the volume regulation of the organism is disturbed by the sudden acquisition of potential edema fluid its presence in tissues may be demonstrated even in dogs which do not show palpable edema from sodium chloride alone.

When sodium bromide was given to dogs by mouth well marked edema developed in most animals. Since bromides are not as easily excreted as chlorides we interpret the production of a salt edema in this case as an instance of providing the organism with more potential edema fluid in a given time than could be eliminated.

essential quantitative relations between the proteins and the inorganic constituents of the various phases of the normal organism and in addition their relative bulk. The former is shown by the height along the ordinate the latter by extension along the abscissa.

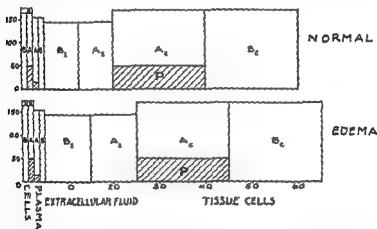


FIG. 117.—A chart to illustrate the relations of water and electrolytes of erythrocytes, plasma, extracellular fluid and tissue cells under normal conditions and after the addition of 5 kg. of edema fluid.

The four essential phases are indicated here as blood cells, blood plasma, extracellular fluid and tissue cells. Equivalent ionic equality is indicated by equal heights of the blocks representing equivalent amounts of anions and cations in each phase. Osmotic equality is indicated by equal total heights of the unshaded areas representing cations and anions in each phase. The existence of a Gibbs-Donnan equilibrium, where it has been shown to apply (i.e. between cells and plasma and between plasma and extracellular fluid) is indicated by the relative heights of the anion areas for cells and plasma and by the heights of the anion and cation areas for plasma and extracellular fluid.

The lower chart, which represents the edematous condition, is in

all respects similar to that of the upper chart save in two essential respects

1 The plasma protein concentration is lower and the base bound by the plasma proteins is proportionately decreased

2 The magnitude of the extracellular fluid phase is increased

This chart is presented in order to emphasize again the fact that the volume of one phase may be markedly altered without essentially changing the ionic or osmotic relationships in the other phases

**Conclusions**—1 Edema is an exaggerated condition of the normal process of filtration of fluid from the blood plasma through the capillaries

2 Its formation is favored by a condition of alkalosis and alkalinizing salts

3 Its formation is impeded by a condition of acidosis and acidifying salts

4 The Gibbs Donnan distribution law does not aid directly in accounting for the changes in edema accompanying acidosis and alkalosis.

5 The role of sodium chloride is passive. Even when factors are favorable for edema formation it can occur only to the extent that salt and water are available. It is suggested that direct analysis of tissues for sodium chloride and water provides a means of quantitatively studying the extent of edema in experimental animals

The important questions of how hydration of the proteins influences water movement within the organism and how changes in reaction and the concentration of ions in the environment influence the degree of hydration have not been dealt with in this discussion. That they must ultimately be taken into account in any complete description of the relation of salts to edema is of course appreciated

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# CHAPTER XXVIII EDEMA IN DOGS FOLLOWING SODIUM BROMIDE ADMINISTRATION \*

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AND

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## BROMIDE EDEMA

WHILE the production of experimental edema in normal dogs by NaCl administration by mouth unaccompanied by other procedures has not been observed as far as the authors are aware it has been found that the closely related salt sodium bromide will produce a well marked edema in most dogs. The sodium bromide must be given in fairly large doses 1 to 2 gm. per kilo per day accompanied by an adequate supply of water. The edema may appear on the second day but usually is not marked until the fourth or fifth day following the initial administration of the salt. It is always present in the extremities and frequently in the tissues around the head and scrotum. Ascites however has never been observed. Increase in size of the extremities increase in weight and a shortened disappearance time of the wheal produced by intracutaneous injections of NaCl or NaBr accompany the edema.

In the hope of detecting with greater accuracy the time of onset of water retention the technique used by Newburgh in his studies of water balance on patients was adapted for use with dogs. A scale was used upon which the dogs could be weighed with an accuracy of 5 gm. each day. The water and food intake and the water and feces output were measured. The water content of the food and feces was also determined. From these data the water balance for twenty four hour periods could be estimated.

Using this technique it was possible to follow the change in water balance with greater accuracy. For example a positive water balance amounting to 500 to 750 gm. of water was found present usually about the third day after the administration of sodium bromide was begun. At this stage palpable edema and a shortened disappearance time of the wheal produced by both NaCl and NaBr

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injected intracutaneously were noted. A gain in weight and water retention appeared before the edema was palpable. A loss of weight but not a corresponding loss of water usually occurred as the result of failure of the animals to eat food after three days of bromide administration. The edema often was even more marked at this time. It is noteworthy that the administration of NaCl seemed to accelerate the disappearance of the edema. The incidence and extent of the edema observed in a series of dogs are given in Table 79.

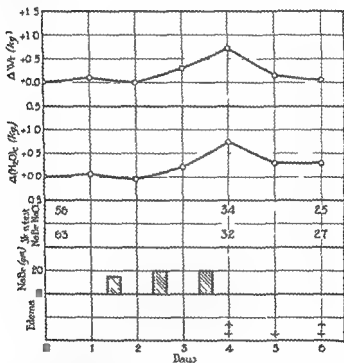


FIG. 118.—The changes in weight and water balance occurring in a dog given sodium bromide by mouth. The disappearance-time of the wheal produced by the intracutaneous injection of salt is indicated in minutes.

The fact that edema was produced in many but not all dogs (13 out of the 17 used developed edema) suggests that a tendency to edema is characteristic of this species as well as of man. That the edema was not merely incidental to the depression produced by the bromides is shown by the fact that dogs previously showing edema upon bromide administration failed to develop it when kept in a comparable state of depression by barbital and given large

amounts of NaCl and water. In view of these results it is of course remarkable that edema is not encountered in man upon bromide administration. It is possible that determinations of the water balance of patients on bromide therapy might at times reveal water retention.

TABLE 79—INCIDENCE AND EXTENT OF EDEMA IN DOGS STUDIED

Dog No.	Medication		Day of first appearance of edema after beginning human diet	Duration of edema, days	Thickness of skin	Pressure			Swelling of scrotum	Day of death after beginning bleeding	Cause of death
	NaCl	NaBr				Fore-limbs	Hind-limbs	Breast			
3A	+	+	6	4	+	+	+	+	+	Alve	
4	+	+	6	2	+	+	+			Alve	
7	+	+	6	8	+	+	+			11	Edema on ho-
9	+	+	6	8	+	+	+			11	bronchopneumonia
10	0	+	7	3	+	+	+	0	0	13	bronchopneumonia
11	+	+	7	3	+	+	+	0	0	13	ill
12	+	+	4	3	+	+	+			5	
13	+	+	4	3	+	+	+			Alve	
14	+	+	5	4	+	+	+			Alve	
15	+	+	5	4	+	+	+			Alve	
16	+	+	5	4	+	+	+	0	0	Alve	
17	+	+	5	4	+	+	+	0	0	Alve	
18	+	+	5	4	+	+	+	0	0	Alve	
19	+	+	5	4	+	+	+	0	0	Alve	
20	+	+	5	4	+	+	+	0	0	Alve	
21	+	+	5	4	+	+	+	0	0	Alve	
22	+	+	5	4	+	+	+	0	0	Alve	
23	0	+	2	2	+	+	+	0	0	4	Bronchopneumonia
24	0	+	3	4	+	+	+	0	+	Alve	

**Electrolyte and Water Changes in Bromide Edema.**—Chemical studies of the blood have revealed the following changes following NaBr administration. The total halide concentration of the serum rose as did that of the erythrocytes; the bicarbonate and pH showed no particular change. Of great interest from the standpoint of ionic distribution is the fact that soon after bromide administration the bromide concentration in the cells rose to a value in excess of that expected from the application of the Van Slyke-Wu and McLean equations—in fact in some instances twice as much bromide has been found in the cells as in the serum, whereas 0.7 as much was anticipated.<sup>1</sup> This occurred at the expense of the chloride concentration of the cells. The total halide distribution ratio remained normal. The only explanation offered for this phenomenon is that a portion of the bromides may displace chlorides from chemical combination within the cells.

No satisfactory explanation for the edema encountered in dogs after sodium bromide administration has been found. All that we

may say at the present time is that given a situation in which the rate of NaBr absorption exceeds the rate of NaBr excretion certain electrolyte and water changes may be expected. The increased cation concentration in the plasma leads to a lowered total halide ratio and water passes from blood cells to plasma to restore osmotic equilibrium. This would bring about a lower plasma protein concentration leading to a disturbance in the balance between hydrostatic pressure and osmotic pressure. Concomitantly there will tend to be passage of water and salts from the plasma phase to the extracellular fluid phase until equilibrium is again established. Due to the increased concentration of base and electrolyte in the extracellular fluid a redistribution of anions and water between the tissue

### NaBr administration

**Effect of Acidosis on Bromide Edema.**—In experiments in which an acidosis was produced in dogs by both  $\text{NH}_4\text{Br}$  and  $\text{NH}_4\text{Cl}$  followed by NaBr administration we have not observed any palpable edema. Under conditions of acidosis a higher distribution ratio of both bromides and chlorides between serum and cells was found than when the acid base balance was normal. This is in harmony with the distribution changes predicted by the Van Slyke Wu and McLean equations.

Reasoning as in the case of the relation of acidosis to NaCl edema the following changes may be pictured as having occurred. The acidosis led to a diminution in the amount of base bound by the serum and blood cell proteins. This in turn led to an increase in the distribution ratio of chloride and bicarbonate between the cells and serum and to the subsequent passage of water from the serum into the cells. In the case of the system tissue cells-extra

### fluid phase

**Effect of Alkalosis on Bromide Edema.**—A comparison has been

made fed was excreted under normal conditions only 35 per cent was excreted in the same time (about eight days) under conditions of alkalosis. It is felt that these experiments may throw some light on the question of why edema is more apt to occur following salt administration under conditions of alkalosis than when the acid base balance is normal.



The water balance in dogs with alkalosis following intensive sodium bromide administration has not yet been carefully studied

**Conclusion** —1 The administration of sodium bromide by mouth to dogs leads to a generalized edema without ascites

2 Measurements of water balance indicate that there is water retention prior to the appearance of palpable edema

3 The influence of experimental acidosis and alkalosis on bromide edema is discussed

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## CHAPTER XXIV RECENT DANISH WORK ON EDEMA

By POLL BRANDT RICHBERG PH D

**Introduction** Albuminuria — In practically all diseases of the kidneys, albuminuria is one of the symptoms. The loss of protein is usually associated with pathological processes in the kidney itself, but may occur even when no lesion of the kidney can be demonstrated (orthostatic albuminuria). What is the origin of this protein?

When inflammation or degeneration is going on in the glomeruli these processes may give rise to destruction of cells, the protein content of which may be expelled into the tubules along with disintegrating leukocytes and thus give rise to albuminuria. Most of the urinary protein has however another origin—from serum proteins excreted through the glomeruli. That this is so, may be inferred from various circumstances. It is often possible to demonstrate albumin in the glomerular capsule and the proteins present in the urine can in no way be distinguished from those of blood. Geil,<sup>2</sup> of the Rigshospital, in Copenhagen gives the result of a series of experiments on the physico-chemical properties of the proteins of both blood and urine. His results are that their behavior toward precipitation with ammonium sulphate is the same and that the precipitation is influenced in the same way by hydrogen-ion concentration and the concentration of the protein. He moreover, confirms the result of previous authors—that most of the excreted protein is serum albumin and that only in cases of amyloidosis the amount of globulins is considerably increased, sometimes exceeding the amount of albumin excreted. This is an additional reason for distinguishing sharply between nephroses and amyloidoses. As an indication that the origin of urinary protein is in the blood we may also take the fact that a considerable protein excretion is always followed by a fall in the protein content of the blood. Bing<sup>1</sup> has demonstrated that the concentration of albumin in the urine in nephritis is proportional to the concentration index. This would be very difficult to understand if creatinine and albumin were not excreted by the same process, viz, filtration of the glomeruli. It further means that in evaluating the excretion of albumin, emphasis should be put not on the concentration but on the absolute amount excreted.

The reason for the excretion of protein is of course clear when the glomeruli are damaged to such an extent that the changes can be demonstrated histologically. When the epithelium in glomerular nephritis is highly altered the glomerular capillaries partly coalesced partly injured so that blood corpuscles may pass through the wall it is no wonder that albumin may also pass through. And that albuminuria may arise through stasis is also understandable when we consider how dependent the capillaries are on the blood flow, how rapidly they answer to a reduction in their blood supply by dilatation and increased permeability.

Much more difficult to understand is the albuminuria of nephroses and those are just the cases where the excretion of albumin is most prominent. Here we have no disturbance of the blood flow and damage to the glomeruli is usually absent or when demonstrable is only slight. It is tempting to seek the cause of the changed permeability not in the epithelium itself but in the composition of the blood flowing through the glomeruli.

It is becoming more and more common to regard nephroses not as a local kidney disease but to see in the changes of the kidney function only a symptom of an underlying general disease with disturbances in the lipid system of the organism—an almost constant finding is cholesterinemia. Rusznak and Nemeth<sup>18</sup> have shown that a kidney perfused with a fluid containing serum protein will excrete protein if saponin is added to the perfusion fluid and that the excretion is stopped when a saponin free calcium rich perfusion fluid is later used. The same has been shown by other authors to hold for ultrafilters. We may perhaps hope to find an explanation for the albuminuria of nephroses in a similar mechanism. The albuminuria leads already said to a lowering of the protein content of the blood and in this lowering we see like Epstein<sup>2</sup> the cause for the edema.

### EDEMA

**Types of Edema.**—By edema we understand an abnormal retention of water in the body outside the circulatory system. When we define edema in this way we have to distinguish sharply between two different edemas: intracellular and intercellular. If the water is retained intracellularly because of disturbed metabolism of the cells we shall only be able to demonstrate an edema by a gain in weight and swelling of the limbs but we know very little about the extent to which this really occurs. Large amounts of water may no doubt be present in the intercellular spaces producing a swelling but not making itself manifest as water—an intercellular edema may in this way be taken for an intracellular edema. In standing quietly in an upright position 300 to 400 cc of water may be filtered into the feet and the lower part of the legs without

producing any symptoms beside swelling. The existence of true intracellular edema can be regarded as established, but so far we know nothing about its mechanism. Intercellular edema is much better known and it is the pathogenesis of this we shall discuss here.\*

**Factors Conditioning Intercellular Edema**—The Danish work on this problem arose out of the study of the physiology of capillaries carried on by Krogh.<sup>9</sup> Concluding from Starling's<sup>17</sup> classical work on absorption of fluids that it was the equilibrium between the hydrostatic pressure in the capillaries and the colloid osmotic pressure in the blood which determined the direction of water movement through the capillary walls Krogh undertook a study of these two factors.

For the study of the colloid osmotic pressure two micromethods were developed with which it is possible to determine in about six hours the osmotic pressure of plasma with an accuracy of plus or minus 5 cm H<sub>2</sub>O and using less than 1 cc of plasma for the determination.

The results with regard to the colloid osmotic pressure may be summarized as follows. The normal colloid osmotic pressure of human blood is on an average 380 mm. Fibrinogen exerts no measurable pressure. Plasma and serum give the same value. The fraction of protein with the smallest molecule is responsible for a large part of the pressure. As soon as a membrane is not completely tight to protein there is a large drop in the pressure measured.

The results with regard to the capillary pressure were that capillary pressure depended on two factors: (1) The friction to be overcome on the way back to the heart and (2) the pressure of the venous blood column from the heart to the place where the measurement is made. The latter factor is the dominating one as soon as we deal with regions lying below the heart since that part of the pressure which is due to the friction in the vessels is less than 10 cm of water. The part played in the capillary pressure by the hydrostatic pressure of the blood column is however very variable depending on the muscular movements of the subject and the efficiency of his vein valves.

## CLINICAL STUDIES OF EDEMA

**Nephrotic Edema**—The plan of Krogh was now to study the balance between colloid osmotic pressure and capillary pressure under different circumstances and among other things it was planned to study also clinical cases showing edema. One of the

\* Only the Danish work or work directly connected with it is reviewed here. Further information on the subject may be found especially in Gowers's\* important papers and in Meyer's\* review.

## RECENT DANISH WORK ON EDEMA

first cases which were examined by Hagedorn, Rasmussen and the author<sup>8</sup> in 1922 was a patient with pure nephrosis. He had considerable edema of the legs and large amounts of ascitic fluid, so that several liters could be emptied at intervals of a few days. His urine showed an albuminuria varying between 2 and 3 per cent. His blood showed a protein content of 5 per cent against the normal 7.5 to 8 per cent. When we determined the colloid osmotic pressure of the blood we found, however, that this was only 100 mm of water against the normal 350 to 400. This reduction in colloid osmotic pressure was far greater than could be

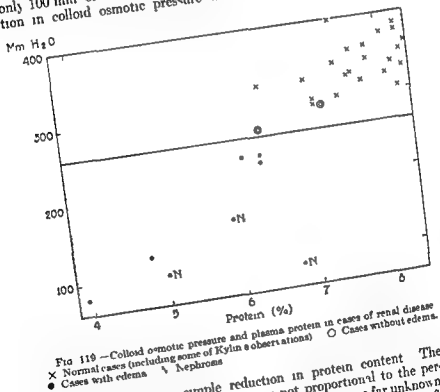


FIG. 119.—Colloid osmotic pressure and plasma protein in cases of renal disease.  
 x Normal cases (including some of Kylin's observations) o Cases without edema.  
 • Cases with edema N Nephrosis

accounted for by a simple reduction in protein content. The colloid osmotic pressure of protein is not proportional to the percentage of protein in solution, but varies for reasons so far unknown, in such a way that the pressure per per cent of protein—the specific osmotic pressure we call it—is higher, the greater the protein concentration is. At a protein concentration of 5 per cent the specific osmotic pressure should be about 37 mm water against a pressure of about 46 mm per cent at the normal protein concentration of plasma (Fig. 119).  
 The 5 per cent protein found in the blood of the nephrotic patient should therefore, exert a pressure of 185 mm, whereas it actually

exerted only 100 mm. This indicated that besides a mere quantitative reduction in concentration the proteins of the blood had been changed so that the remaining molecules had less osmotic activity. We now studied the urine. A sample of urine with a protein percentage of 2.8 showed a colloid osmotic pressure of 240 mm. This was three times as high a specific pressure as a blood with this protein content would show and from this we drew the conclusion that the cause of the edema was to be looked for in the following successive events.

The primary change is that the glomeruli for some unknown reason become abnormally permeable but only so much that the smallest and therefore most active protein molecules are filtered out. As a result of this the protein content of the blood is lowered and changed in such a way that a large reduction in the colloid osmotic pressure results and with this reduced in the colloid water the capillary pressure will be higher than the osmotic pressure in most places in the body, especially in the lower part and in the portal system. Water will be filtered out and edema results. As the loss of protein was up to 20 gm a day or about one seventh of the present total amount of plasma protein and as he showed no sign of nitrogen retention we replaced the protein poor diet with a protein rich one.

Following this case which was reported briefly in the first edition of Krogh's book on capillaries a number of cases have been studied by Krogh's co-workers all showing the same type of lowering of colloid osmotic pressure though generally not so pronounced. Several investigators have published papers confirming the results but the author will discuss only the results obtained by Kjerfve and Nakazawa with various co-workers (1914).

In a case of nephrosis they found a pressure of only 89 mm of water with a protein content of 6.77 per cent which ought to have given 293 mm pressure that is it gave only one-third of what was expected. The urine contained 1.60 per cent protein with a pressure of 181 mm (instead of 47 mm). In this case it is even more evident that the smaller active molecules had been excreted. Kjerfve and co-workers studied a number of cases of edema associated with kidney diseases and found that whether it is acute nephritis, chronic nephritis or nephrosis edema does not occur until the colloid osmotic pressure of the blood is lowered to about 240 mm of water. The material of Kjerfve and Nakazawa more over gives the very important information that while the specific osmotic pressure of the plasma decreases when the plasma is diluted the specific osmotic pressure of the urine proteins is higher the smaller the protein percentage. This means that the smaller the percentage of protein in the urine the smaller are also the molecules excreted.

This is evident  
permeability of  
conclusions draw

and we may regard it as proved that in kidney cases edema is due to a lowering of the colloid osmotic pressure of the blood. In no case is it necessary to assume any damage to the capillaries since the edema fluid shows only a small amount of protein with a negligible osmotic pressure.

Iversen and Nakazawa studied next the pathogenesis of edema in other diseases.

**Cardiac Edema.** The question was whether the explanation here given would hold also for other forms of edema. Could a lowering of the colloid osmotic pressure of the blood be demonstrated—and was an eventual lowering sufficient to explain the formation of the edema?

A number of patients with cardiac edema were examined first

on the basis of this lowering alone but in other instances the lowering though distinct was hardly sufficient to explain the formation of edema. In 1 case for instance on different occasions on

unchanged as the pressure gradually fell to 20 mm.

There is a distinct relation between the colloid osmotic pressure and

in these patients. The capillary blood pressure is in many cases increased because the venous return to the heart is insufficient and moreover the capillary walls are injured through the stasis and may be abnormally permeable. The edema fluid of cardiac patients generally contains about 1 per cent protein whereas in nephrotic edema its value is always below 0.5 per cent. The explanation of the edema in cardiac patients is therefore to be found in a combination of the following causes: decreased colloid osmotic pressure of the blood, increased capillary blood pressure and to some degree increased permeability of the capillary walls.

Iversen discusses the cause of the decrease in the protein content of the blood of cardiac patients. In the few cases in which the degree of albuminuria was large enough to allow a determination of the colloid osmotic pressure of the urine it came out that here

also the small protein molecules were the ones preferentially excreted. The amount excreted is however usually small and though the loss of protein may go on for months it is hardly possible that this loss together with the small amounts found in the edema can explain the lowering unless the regeneration of the protein is in some way disturbed. As an example which points toward this possibility, Iversen records the following case.

The patient suffered from high grade insufficiency of the heart he had albuminuria and very considerable edema. On November 5 his blood showed 4.81 per cent protein with a colloid osmotic pressure of 173 (specific pressure 36). During treatment the albuminuria stopped and from November 23 to December 21 his

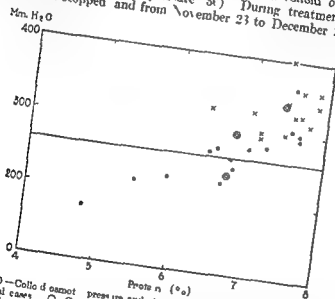


Fig. 10.—Colloid osmotic pressure and plasma protein in cases of heart disease. X Normal cases; O Cases without edema; ● Cases with edema. The line indicates the limit below which edema occurs in renal diseases (See Fig. 119).

urine was free from albumin. His blood proteins during this period increased to values varying around 6 per cent or even higher. However, as late as December 6 when the protein percentage was 6.77 the colloid osmotic pressure was only about 240 mm. This gives a specific pressure of 35 mm against a normal value of 43 which shows that the restoration of the protein content was due chiefly to formation of larger molecules. Iversen seeks the reason for this failure to renew the smaller protein molecules in the stasis of the liver.

In a case of orthostatic albuminuria the pressure of the blood colloids was on the other hand quite normal showing that here the formation of protein could compensate for the excretion.



Iversen now proceeded to study other forms of abnormal fluid collections in the body. This work will be mentioned also because the results obtained confirm the whole view.

**Ascites**—Iversen maintains that the ascites combined with stasis of the liver and tuberculous ascites are of quite different origin. When a protein rich fluid is formed outside the capillary system the equilibrium becomes seriously disturbed. In the abdominal cavity we have then 2 forces trying to drive water out of the capillaries the capillary blood pressure ( $P_c$ ) and colloid osmotic pressure of the protein-containing fluid outside ( $COP_o$ ). As forces trying to drive water into the blood we have the colloid osmotic pressure of the fluid outside ( $P_o$ ) and the hydrostatic pressure of the fluid outside ( $COP_o$ ) and the hydrostatic

As long as  $P_c + COP_o = P_o + COP_o$  no movement of water will take place but if the two former forces  $P_c$  and  $COP_o$  are increased so that their combined pressure is higher than that of the other two fluid will be pressed out and ascites formed. Of these four pressures we can measure the two arising from the colloids and we can measure the pressure under which the fluid in the abdominal cavity stands. We cannot measure the capillary pressure but we can maintain that normally it must be very low as one can see cases with a colloid osmotic pressure of the blood of only 100 mm of water without any formation of edema. The factor which changes most is the colloid osmotic pressure of the ascites fluid. In a series of 12 cases Iversen finds values between 25 and 264 mm so that 2 cases of hepatic cirrhosis gave values respectively of 25 and 29 mm of water, while the colloids in the ascites of 3 cases of tuberculous nature gave 195, 196 and 264 mm pressure. The values were high in the cases of cardiac cirrhosis also. When the colloid osmotic pressure in the ascites fluid is as low as 30 mm of water this factor is of small importance in the pathogenesis of the ascites and Iversen is of the opinion that the cause in these cases is to be found in the stasis of the liver which produces a considerable increase in the blood pressure in the peritoneal capillaries.

Iversen finds that an ascites fluid which is renewing itself after a puncture contains less protein than the fluid emptied out at the puncture. His idea is that as long as only relatively small areas of capillaries are injured the fluid which is filtered out through these areas and which contains a low concentration of protein is concentrated by reabsorption of water in those capillary areas which are still normal. In this way the fluid may be concentrated until its colloid osmotic pressure is about 200 mm when further reabsorption is impossible because equilibrium is reached. Is larger capillary areas become involved in the stasis reabsorption takes place to a less and less extent and the concentration of protein in

the ascites fluid is decreased. A high percentage of protein is thus looked upon as a sign of relatively normal circulation in some areas. For such cases where the main cause of the ascites seems to be an increased capillary pressure due to liver stasis Iversen thinks that splenectomy is indicated and has tried this with success.

Among the other diseases with abnormal collections of fluid in the body Iversen together with Hecht Johansen<sup>7</sup> studied a number of patients with fluid in the thoracic cavity due either to cardiac disease or pleuritis.

**Cardiac Hydrothorax**—In cardiac hydrothorax these authors find that the transudate contains a rather low percentage of protein but that the percentage is increased if the circulation of the patient is improved through treatment. If so a reabsorption of water begins a reabsorption which goes on until equilibrium is attained. Hence the better the patient becomes, which means the lower his capillary pressure falls—the higher will be the protein content of his hydrothorax fluid.

An example showing this is the following. A patient with degenerative myocarditis and hydrothorax the fluid of which possesses a protein content of 1.48 per cent. After emptying new fluid is formed which has 1.38 per cent protein and a few days later 1.59 per cent. On July 21 and 23 the patient receives valyrgan and on July 23 the protein content is 3.10 per cent. Valyrgan is given again on July 26 and the protein increases to 3.45 per cent. When no valyrgan is given for four days the protein decreases to 2.83 per cent but rises to 3.65 per cent after a new valyrgan injection. There is little doubt that the variations in the protein content of the hydrothorax fluid in a case like this are due to reabsorption of water. This reabsorption can go on only until equilibrium is reached which will happen as the protein content approaches 4 per cent. (The highest observed value was 4 per cent.)

**Tuberculous Pleuritis**—This value of 4 per cent protein is much less than the concentration often observed in tuberculous pleuritis. Here the normal values vary between 3.65 and 6.31 per cent with an average of about 5 per cent. This concentration is so high that it is impossible to account for it by reabsorption and the authors maintain that here as in the cases of tuberculous ascites the capillaries are so severely damaged by toxins that they are permeable to most of the proteins of the blood.

**Edema of Beri beri**—Takazawa has added a disease to the many already known in which we can demonstrate disturbance in the equilibrium of capillary blood pressure and colloid osmotic pressure of the blood as factors at least contributing to the production of edema. Together with Seki and Inawashiro<sup>14</sup> he studied the conditions in beri beri. In this disease one may find cases either with

or without edema. Some stasis is often present. The findings on a number of patients showing edema revealed an osmotic pressure lower than that of those with the dry form. Many of the patients however had edema with a pressure high above the level at which edema would form if lowering of the protein content were the sole cause a fact easily understood because of the stasis existing in these individuals.

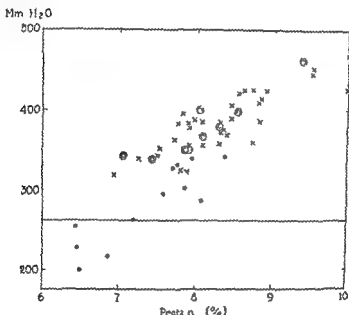


FIG. 191. Colloid osmotic pressure and plasma protein in cases of beriberi. X Normal cases. O Dry form. • Edematous form. Both normal and pathological values from the material of Nakazawa, Seki and Inawashiro.

*Summary* — We may perhaps sum up the results of the studies by saying that the wide variety of disturbances so far investigated in which extracellular edema is known to exist, i. e. kidney diseases, heart diseases, ascites, hydrothorax, anemia and beriberi, it has been demonstrated that there is either

1. Decreased colloid osmotic pressure of the blood
2. Increased capillary pressure
3. Injured and normally permeable capillaries

Or a combination of these factors. In these changes we seek the causes of extracellular edema and we are of the opinion that as long as these three factors are normal extracellular edema will not be formed.

*Effects of Hormones on Edema* — There are many questions yet to be settled, one of which is: What is the mechanism of the undoubted

influence of different hormones on edema? It is well known, for instance, that the institution of insulin treatment is often accompanied by edema formation. It is not yet possible to give an explanation of this, but K $\ddot{u}$ lin has observed a considerable decrease in the colloid osmotic pressure of the blood in the cases which developed edema and in some cases he saw the decrease before the edema developed.

Tada and Nakazawa<sup>18</sup> have performed experiments which have some bearing upon this question. When they inject one of the following four hormones: thyroiodin, pituitrin, insulin or adrenalin, in rabbits they find that in all cases a decrease in the protein content of the blood results. For pituitrin and adrenalin this fall in protein concentration is followed by a decrease in the colloid osmotic pressure of the blood, a decrease which is, however, larger than can be accounted for by the decrease in concentration of the protein.

This seems to indicate that these two hormones exert a direct influence on the proteins of the blood so that the specific osmotic pressure of the proteins is reduced and in *in vitro* experiments the authors also find that this happens. Both adrenalin and pituitrin depress the colloid osmotic pressure of plasma. In spite of this more fluid enters the circulation, an occurrence which the author thinks is due to the dominating effect which these hormones have on the capillary pressure. If capillary pressure in some areas is depressed because of constriction of the arterioles, the equilibrium between the colloid osmotic pressure and the capillary pressure is disturbed and may result in entrance of fluid from the intercellular spaces into the blood, thus producing a dilution of the blood proteins.

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## CHAPTER XXXV

### EXPERIMENTAL NEPHROTIC EDEMA \*

By LOUIS LEITER M D PH D

#### CLINICAL NEPHROTIC EDEMA

THE  
has be  
the as  
nepl r  
is to the credit of Epstein <sup>1 2</sup> Beckmann<sup>3</sup> and others<sup>4 5</sup> to have  
analyzed edema fluids from patients with various diseases and laid  
the foundation for a correlation between the pathogenesis of the  
edema and the protein content of the transudates. Thus experience  
has been fortified by theoretical deductions in regard to the patho-  
genetic mechanism of the edema. An experimental attack upon  
the edema desired. This is  
of importance since earlier attempts to produce edema had centered  
largely upon damage to some excretory organ like the kidney or  
some transportation system like the vascular or lymphatic network.  
The edema fluid itself was not adequately studied. Hence it was  
not recognized that there might be different kinds of edema fluids  
depending upon the method of production. The quantitative aspect  
of edema introduced by Epstein rounded out the more or less quali-  
tative picture derived from observation alone and furnished a  
yardstick by means of which edemas clinical or experimental could  
be classified. Hence we consider the low protein content of

that certain dropsical fluids had a low protein content as revealed  
by their low specific gravity. It is interesting to note that Starling<sup>6 7</sup>  
criticized Cohnheim's theory of the inflammatory origin of renal  
dropsy on the grounds that the low protein content of the edema  
fluid was evidence against that theory. Scattered analyses only  
such as those of Javal<sup>8</sup> on ascitic fluid are found in the literature.  
Volhard<sup>9</sup> described the transudates in nephrosis as almost a

\* From the Lasker Foundation for Medical Research and the Department of  
Medicine University of Chicago

## EXPERIMENTAL NEPHROTIC EDEMA

physiological salt solution --an apt expression. In 1914 Epstein<sup>10</sup> presented the first systematic analysis of different types of edema fluid pointed out the very low protein content of certain of these and a little later<sup>11</sup> correlated these findings with Starling's physiological considerations as to the rôle of the osmotic pressure of the colloids of the plasma in fluid exchange. Beckmann,<sup>4</sup> Iodor and Ischer,<sup>12</sup> Osborne<sup>13</sup> Falta and Quittner<sup>14</sup> and Goyert<sup>15</sup> have published series of determinations establishing the existence of edema fluids with a protein content of about 0.1 per cent or less in the case of subcutaneous anasarca and about 0.5 per cent or less for ascitic fluid. Table 80 presents a summary of their findings.

TABLE 80 --THE LOW PROTEIN CONTENT OF CLINICAL NEPHROTIC EDEMA FLUIDS

Author	Disease	Protein per cent
Epstein	Nephrotic glomerulonephritis	0.008 to 0.785
Javal <sup>16</sup>	Latent nephrosis	0.200 to 0.400
Volhard <sup>17</sup>	Nephrosis	0.075 to 0.100
Beckmann	Nephrosis amyloidosis	0.010 to 0.310
Fodor and Fischer <sup>18</sup>	Nephrotic glomerulonephritis	0.010 to 0.140
Hellmuth <sup>19</sup>	Nephropathy of pregnancy	0.070 to 0.180
Falta and Quittner <sup>14</sup>	Hunger edema	Less than 0.14 in 10 cases out of 20
Mense and Zondek	Hunger edema	0.067 to 0.100
Jansen	Hunger edema	0.118
Fodor and Fischer	Hunger edema	0.018 to 0.067
Landis and Leopold	Hunger edema	0.008
Kobayashi <sup>20</sup>	Inanition edema	0.040
	Enteritis	Less than 0.5 in most cases
	Beri beri	0.7 in one-half of cases

**Nutritional Edemas as Nephrotic in Type** --During this period of active investigation of clinical edema and related problems the nutritional privations of the World War reached their climax in the widespread occurrence of the so-called war edema or famine dropsy. This form of edema seemed to be independent of demonstrable renal or cardiac disease. It was promptly classified as a nephrotic type of edema because it had many clinical features in common with the nephrotic edema of Bright's disease. Most important the edema fluid had the same low protein content. Thus it appeared logical to include other nutritional disturbances under the same heading. When obviously a purely nutritional disturbance. When the edema was ever the edema fluids were properly obtained and analyzed their protein content was found of the same order of magnitude as in nephrosis. The extrarenal nature of the intercellular accumulation of fluid was beyond doubt. One may refer to the list of nephrotic edemas the anasarca seen in cachectic states of various origins in pernicious anemia in pregnancy in beri beri in the complicated nutritional anemias common in India and China in undernourished

diabetics, in patients with severe diarrheas or short circuited alimentary canal with unpaired absorption, and in the nutritional maladjustments occurring during infancy and early childhood. In many of these conditions the edema may be only a minor symptom, in others the entire clinical picture may be dominated by it, and an understanding of the nature of the disturbance in the water balance may lead to more efficient therapy. Table 80 shows that all these edemas have the same low protein content as the dropsical fluid in nephrotic Bright's disease including amyloidosis.

**Distribution of Nephrotic Edema**—It has been the custom to

around but shifts to the thighs, lower back and lateral abdominal walls when the recumbent position is assumed. The face is rarely involved. On the other hand, renal edema ordinarily affects the face, especially the loose tissues of the eye-lids, the back of the hands and forearms, the scrotum and labia, in addition to the lower extremities. Renal edema is therefore, said to be more or less independent of gravity. But, as a matter of fact even nephrotic edema is to a considerable extent influenced by gravity. In mild cases the edema is usually noticed only in dependent portions, i. e., about the feet or ankles when the patient is up and about the external genitalia, inner aspect of the thighs and over the sacrum after the patient has been in bed for some time. The rapid dis-

the night, edema accumulates in the relatively low face and it is common to find more swelling on the side of the face that was lowermost.

forearms. O

therefore, the

cardiac edema. All types of nephrotic edema, regardless of their origin, tend to predominate in dependent regions of the body and tend to favor areas where the tissues are soft, loose and yielding.

The fluid shifts relatively rapidly with change of position. It is

ties, particularly the peritoneal spaces, are frequently filled with transudate, and there is at times evident an inverse relationship between the amount of ascites and the extent of edema in the lower extremities, depending upon the position of the patient and the corresponding effect on the efficiency of the circulation.



Unlike other forms of edema, nephrotic edema very rarely becomes dangerous to life as a result of involvement of the respiratory tract or the brain. Edema of the brain hardly ever occurs. In a case reported by Murphy and Warfield<sup>53</sup> it was apparently the immediate cause of death. In general, one may say that nephrotic edema is harmful insofar as it *impedes locomotion, interferes with the movements of the diaphragm and intercostal muscles, impairs capillary circulation and furnishes a culture medium for pneumococci and streptococci*. These handicaps to the patient's daily life do not exist when the edema is of moderate extent and there is little fluid in the serous cavities. However, the underlying disease, such as nephritis, malnutrition, amyloidosis, etc., may be the source of a number of distressing symptoms unrelated to the presence of edema.

**Association With Decreased Concentration of Plasma Proteins —** Regardless of the disease or condition associated with nephrotic edema, there is always a definite decrease in the concentration of total plasma or serum proteins and usually a striking change in the

extreme decrease in plasma-protein levels and the most marked reversal of the  $\frac{\text{albumin}}{\text{globulin}}$  ratio are found in such conditions as nephritis, nephrosis and amyloidosis, where there is actual excretion of large amounts of formed proteins. The few carefully studied cases — to fall undi-  
retion

of the plasma proteins and prevents their proper replenishment. In the various types of nutritional edemas, including those seen in the anemias and in cachectic and malignant states all degrees of reduction in the concentration of the plasma proteins may be found. The data in Table 81 illustrate this point. No attempt

analysis. In general, it is rare to find any considerable degree of nephrotic edema when the total plasma protein concentration chemically determined, is above 5 per cent and the albumin fraction above 2 per cent. At any rate the response of edema to therapeutic

measures is more prompt and permanent at or above these levels for total protein and albumin than below. When the plasma proteins are markedly reduced and albuminuria persists unchecked, the edema is likely to be a stubborn manifestation not yielding to diuretic measures. Fortunately such cases of extensive anasarca are rare nowadays owing to the more intelligent recognition and treatment of the early stages. The formation of large quantities of a transudate may itself appreciably deplete the plasma proteins to a critical level in spite of the low percentage of protein in the fluid. The repeated removal of ascitic fluid by paracentesis may be as severe a drain upon the plasma proteins as a moderately severe albuminuria.

TABLE 81.—THE PROTEIN CONCENTRATION OF THE SERUM OR PLASMA IN CLINICAL NUTRITIONAL EDEMA

Author	Disease	Plasma protein per cent
Schittenhelm <sup>21</sup>	Hunger edema	3.94 to 7.0 in 41 cases of 49 (R)*
Janson <sup>20</sup>	Hunger edema	4.0 to 6.4 in 30 cases of 40 (R)
Wolferth <sup>2</sup>	Inanition edema	3.30 to 4.60 (R)
Mosai et al. <sup>2</sup>	Beri beri	Less than 7.0 (R)
Peters et al. <sup>14</sup>	Advanced pulmonary tuberculosis	1.68 to 5.63
	Intestinal tuberculosis emaciated	1.44
	Jejunocolic fistula	1.69
Meulengracht et al.	Pernicious anemia	5.0 to 7.31 (R)
Palmer <sup>1</sup> †	Gastro-jejunocolic fistula	7.1 to 4.27
Landis and Leopold <sup>1</sup>	Tuberculous enteritis	3.6 (R)

## HISTORICAL REVIEW OF EXPERIMENTAL EDEMAS

**Older Theories of Renal Edema and Their Influence Upon Experimental Work**—Bearing in mind the above discussion of clinical nephrotic edema the shortcomings of the earlier experimental work become manifest since no clear division was drawn between the different kinds of so called renal edema and little effort was expended to determine the quantitative nature of the edema fluid with the exception of the chloride content. To a large degree, the experimental attack upon edema followed the theoretical concepts laid down by the great clinicians of the nineteenth century who interested themselves in the problems of Bright's disease. It may be appropriate to sketch briefly their theories of renal edema and to show how certain experimental edemas were bound up with these ideas. The fruitfulness of these viewpoints of busy, but physiologically minded clinicians to the investigators in contact with them is well illustrated in this field of medical research.

\* (R) indicates refractometric analysis. Chemical methods were used by the other authors.

† Unpublished data of Dr W. L. Palmer, Department of Medicine, University of Chicago.

## EXPERIMENTAL NEPHROTIC EDEMA

Bright,<sup>7</sup> dealing largely with the subacute and chronic forms of renal disease, was struck by the quantitative significance of the proteinuria and was probably not surprised to find the decrease in plasma proteins. He assumed that the thin, watery or "hydreic" condition of the blood plasma made it more easily filtrable into the tissue spaces. Curiously enough, the reverse of this process, the return of fluid from the tissue spaces into the blood, was apparently not related to the altered composition of the blood. Thus Bright missed the opportunity that Starling grasped in a flash of genius some sixty years later. Bright's concept of hydreia as due to a decrease in plasma proteins was, however, correct, although almost a hundred years elapsed before direct proof was brought forward in the work on plasma-volume and plasma-protein concentration by the Van Slyke group.<sup>8</sup>

Stewart<sup>9</sup> and Bartels<sup>10</sup> were more impressed by the oliguria associated with periods of nephritic edema and assumed the former to be the cause of the latter by way of "hydreic plethora" or a true increase in plasma volume.

Senator<sup>11</sup> while recognizing the inadequacy of Bright's theory for the edema of acute nephritis in which dropsy often occurs early in the disease before much plasma protein can have been lost with the urine realized equally well that Bartels' reasoning as to the importance of oliguria was less applicable when the chronic forms of renal edema were considered. But like his predecessors he searched for an all-embracing concept to explain all forms of renal edema on a uniform basis. He extended the idea of capillary damage in renal disease to apply to the glomerular capillaries alone. In this way, increased capillary permeability readily explained the edema of acute glomerulonephritis and could be stretched to cover chronic renal edemas as well although Senator admitted that "hydreia" (low plasma protein level) was also a factor in the anasarca of amyloidosis and other conditions associated with wasting.

These theories of Bright, Bartels and Senator are all partially correct—Bright's theory, when applied to chronic nephrotic edema, Bartels' theory, when considering the edema of acute oliguria and anuria of non-inflammatory origin (e.g., mechanical obstruction of the urinary tract, mercurial poisoning, etc.) and the true renal retention of water in terminal uremic states, Senator's theory, when used to explain the early edema of acute glomerulonephritis. These three factors—hydreia, insufficient excretion of water and capillary damage are as important today as fifty years ago.

**Experimental Edema as the Result of Vascular Damage and Increased Capillary Permeability**—The experimental study of edema proceeded *pari passu* with the development of the above theories with the exception of the view of Richard Bright, which was not

adequately investigated. Most of these experiments have become classical and need little description. Bartels' theory of hydremic plethora as the cause of renal edema was put to the experimental test by Cohnheim and Lichtheim,<sup>9</sup> Magnus<sup>49</sup> and others. In experiments involving the intravenous injection of enormous quantities of fluid, the rôle of hydremic plethora or increased plasma volume, was found to be a subsidiary one in the production of edema while vascular damage, brought about by various chemical or physical irritants, was shown to be of prime importance. In short, Senator's idea concerning the increased permeability of damaged capillaries was confirmed and the analogy was drawn with the changes in the cutaneous capillaries in scarlet fever. In none of these studies was the edema fluid analyzed for protein but the nature of the procedures seem to leave little doubt but that the fluid was a protein-rich exudate and therefore entirely unrelated to nephrotic edema.

**A The Non-nephrotic Edemas —1 Uranium Edema**—Senator's view was found further experimental support in the work done on the toxic nephropathies especially uranium poisoning. Richter<sup>50</sup> showed that under certain conditions uranium nitrate could produce edema in association with renal damage whereas other poisons

demonstration of what many had suspected ever since the work of Cohnheim and Lichtheim namely that renal damage was one factor only and at times a relatively unimportant one in the production of so-called renal edema, while general capillary injury was of primary significance. Of course the oliguria, the extent of extrarenal loss of fluids and the supply of water and salts were found to be important accessories in the production of edema by uranium nitrate. These factors however were of importance in all types of edema. It should be noted that the most successful results were obtained in the rabbit—an animal which does not perspire and cannot vomit and, therefore, at a serious disadvantage when its kidneys are excluded from function and something like 50 cc of water per kg of body weight are given to the animal. It would seem that Bartels' theory of renal retention of water would apply to these experiments just as it undoubtedly does in nephrectomized animals.

**High Protein Content of Uranium Edema Fluid**—In connection with uranium edema one finds the first systematic analyses on the protein content of the edema fluid usually ascitic. Georgopoulos<sup>51</sup>

fibrinogen content and point to considerable injury of the capillary endothelium. In the last few years more data on uranium edema have become available through the repetition of this work by French and Belgian investigators. Thus Garnier, Schulmann and Marek,<sup>19</sup> Nau<sup>24</sup>, Schulmann and Marek<sup>24</sup> and Govaerts<sup>25</sup> have reported the protein content of ascitic fluid as between 1 and 4 per cent (Table 82). Obviously one is dealing with an exudate resembling the fluid in a blister more closely than ordinary nephrotic edema fluid.

TABLE 82 — THE HIGH PROTEIN CONTENT OF SOME EXPERIMENTAL EDEMA FLUIDS.

Author	Method	Protein per cent
Georgopoulos <sup>26</sup>	Uranium nitrate	0.34 to 3.85
Garnier et al. <sup>19</sup>	Uranium nitrate	2.60
Schulmann and Marek <sup>24</sup>	Uranium nitrate	2.30
Nau <sup>24</sup>	Uranium nitrate	2.80 to 5.1 (total solids)
Govaerts <sup>25</sup>	Uranium nitrate	1.70 to 3.80
Tainter and Hansel	Paraphenylenediamine	Very high (whole plasma)
Bolton <sup>5</sup>	Partial venous obstruction	6.50 to 7.90 (total solids)
Farnum et al. <sup>4</sup>	Nephrectomy	1.26 to 3.74

■ **Paraphenylenediamine and Mustard Oil Edema** — The physical characteristics and the high protein content of uranium edema fluid allow an easy transition to the frankly inflammatory edemas local and more or less general produced by such poisons as paraphenylenediamine and mustard oil. This group of edemas is interesting for three reasons: (1) Because the kidneys are not implicated; (2) because direct vascular damage has been shown to be the mechanism involved; (3) because this group lends itself to rigidly controlled experiments. The work of Hirschfelder<sup>27</sup>, Lunter and Hanzlik<sup>7</sup> and Tainter<sup>28</sup> is characterized by strict adherence to the scientific method of controlling one factor after another. These investigators have demonstrated that local capillary injury is the direct cause of exudation while the amount of edema depends upon the mechanical factors of the circulation such as capillary pressure and blood flow. In other words the theories of Ludwig, Cohnheim and Starling have been confirmed. The edema produced in these experiments indicates a marked increase in vascular permeability, the whole plasma passing out of the capillaries to clot in the tissue spaces. Nephrotic edema represents the other extreme inasmuch as no change in capillary permeability to protein is demonstrable except in the glomeruli when there is albuminuria. Nephrotic, cardiac and other non-nephrotic edemas fall between these two extremes.

3 **Experimental Edema by Mechanical Obstruction in the Circulatory or Urinary System or as the Result of Nephrectomy** — Several groups of experiments may be mentioned representing a combination of renal, mechanical and permeability factors in varying degree. Bolton<sup>5</sup> using a method for partial occlusion of the inferior vena

cava above the diaphragm was able to produce in cats a small amount of ascites that persisted or reformed for a few months until collateral circulation was established. This essentially cardiac ascites was rich in solids chiefly protein. The change in permeability here is easy to understand while increased capillary filtration pressure undoubtedly aggravates the situation. Lyon Shafton and Ivy<sup>47</sup> and Farmer Barry Reed and Ivy<sup>48</sup> have produced edema in nephrectomized dogs by the subcutaneous administration of Ringer's solution. The injected fluid is evidently absorbed redistributed by the circulation and deposited in the serous cavities and subcutaneous tissues as true edema. This edema is analogous to the terminal retention of water in patients with contracted kidneys or with complete obstruction of the urinary tract. It may also have some bearing upon the edema developing in acute renal disease with oliguria or anuria. In all of these conditions the same situation must prevail as in the rabbit poisoned by uranium that is fluids must be forced beyond the animal's capacity to dispose of it in the presence of non functioning kidneys. The reason why edema is not more often seen in terminal uremic states with oliguria is probably that the patients are losing more fluids by way of the gastro intestinal tract than they are receiving orally or parenterally. That renal retention of water can play an important role when other sources of elimination are lacking and the intake of fluids is not reduced has been shown by McClure<sup>49</sup> Swingle<sup>50</sup> Adolph<sup>51</sup> and Brugsch Cohen Horsters and Rothmann.<sup>52</sup> These investigators produced marked edema in frogs or tadpoles by tying off the cloaca or both ureters or extirpating the kidneys after which the animals were kept in water. Since the osmotic absorption of water by the frog's skin goes on continually regardless of the requirements of the animal or the capacity of the excretory system to handle the fluid, edema is easily obtained. A better illustration of renal retention of water is difficult to find. Whether in any of these experimental edemas there are significant changes in the volume or composition of the plasma cannot be determined from the published reports.

In regard to the protein content of the edema fluid no data are available on the frogs but Farmer Barry Reed and Ivy<sup>48</sup> have found well over 2 per cent of protein in the ascitic fluid of their nephrectomized dogs indicating a considerable increase in permeability of the capillaries due to unknown toxic agents. This type of edema associated with true urinaemia is not nephrotic in character and should not be correlated with clinical nephrotic edema.

**B The Nephrotic Edemas . 1 Experimental Nutritional Nephrotic Edema in Rats** Up to this point none of the experimental edemas discussed has borne out the fundamental features of nephrotic edema.

A fairly close relationship could be shown between some of these and acute nephritic edema in man the elements of vascular injury and the high protein content of the edema fluid being common to all of them. It was not until the epidemic of war edema began to be understood that attempts to reproduce nutritional edema in experimental animals were carried out. Denton and Kohman<sup>10</sup> and Kohman<sup>11</sup> obtained dropsy in rats which had been kept for several weeks on a low protein (carrot) diet otherwise adequate for nutrition and growth. Increase of protein in the diet led to disappearance of the edema. The fluid intake was found to be an important factor. The edema did not appear until definite emaciation had developed. This observation pointed to an exhaustion of body protein. The significance of this nutritional edema lay in the fact that no toxic agent was involved that might alter capillary permeability. Here a nephrotic edema had apparently been obtained. Mayer<sup>12</sup> obtained similar results. Some years later Frisch

**2 Nephrotic Edema in Monkeys** The edema developing in a long dietary experiment on a monkey reported by Harden and Silva<sup>14</sup> probably falls into the same group. Emaciation was an evident factor. The author has observed instances of spontaneous anasarca in laboratory monkeys. One monkey\* had a definite nephrotic edema with typical low serum proteins and very little protein in the edema fluid. The edema involved dependent portions but was also noticeable on the face in the early part of the morning. It gradually disappeared on a generous mixed diet. Autopsy later on disclosed neither cardiac nor renal pathology. This as far as is known represents the first established instance of nephrotic edema in the monkey. The primary cause of the condition could not be established. Diarrhea occurred intermittently during the period of edema. A detailed study will be published elsewhere.

**3 Experimental Nutritional Edema in Man**—The availability of markedly undernourished individuals in Central Europe during the World War made possible interesting experiments on edema. Thus Falta and Quittner<sup>15</sup> brought on a nephrotic type of edema in emaciated diabetics and non diabetics by forcing fluids and salt along with large amounts of sodium bicarbonate. This regime is not effective in individuals with a normal state of nutrition. Jansen<sup>16</sup>

\* It was through the kindness of Dr. I. S. Falk formerly in the Department of Hygiene and Bacteriology of the University of Chicago that this opportunity was afforded as the monkeys belonged in his experimental stock and he made the original observations.

obtained similar results on an emaciated woman with a malignant esophageal stenosis and a gastric fistula. The low protein content of the plasma in this type of edema is shown in Table 81.

**4 Experimental Bromide Edema in Dogs**—The edema produced in dogs by the combined administration of sodium chloride and sodium bromide, as reported by Hastings and Van Dyke,<sup>26</sup> represents an . . . kidneys. The edema fluid has a low protein content.<sup>25</sup>

### PLASMAPHERESIS

The problem that presented itself in 1925 was the direct production of experimental nephrotic edema without damage to the kidneys or injury to the capillary the forces involved in tissue spaces. Since Ling's<sup>28</sup> classical work on the osmotic pressure of the plasma proteins, evidence had accumulated to prove the connection between albuminuria, low plasma proteins, decreased colloid osmotic pressure of the plasma and the development of nephrotic edema. This sequence was virtually a return to Richard Bright's brilliant guess with the addition of a mechanism for drawing tissue fluids back into the blood. Supported by the determinations of the osmotic pressure of the plasma proteins by the Krogh school,<sup>27</sup> by Govaerts,<sup>21</sup> Schade and Claussen,<sup>22</sup> Rusznýk<sup>24</sup> and others the *Starling-Epstein-Krogh* theory of nephrotic edema, as we may call it, was an enormous advance over the theories of tissue or colloid affinity for water, or of 'increased permeability' to water and salts in only one direction through the capillary. It seemed desirable to attempt to forge the last link in this chain of evidence, that is the production of edema by a rapid and continual loss of plasma protein in an experimental animal. If obtainable, the edema fluid should in accordance with the theory, have a low protein content. This was the crux of the problem and needs emphasis because investigators have overlooked this point to the extent of not determining the protein content of the edema fluid. It was at the suggestion and with the encouraging guidance of Dr. D. D. Van Slyke that work on this problem was begun at the Hospital of the Rockefeller Institute in 1925. The experiments were continued in the Department of Medicine of the University of Chicago from 1927 on, thanks to the generous support and faithful interest of Dr. Franklin C. McLean.

**The Method—Plasmapheresis as a Substitute for Albuminuria**—The method employed consisted essentially in the direct removal of the plasma proteins in dogs by the process of plasma depletion



so successfully employed by the Whipple school<sup>24,25</sup> The dogs were bled from the heart or jugular veins instead of the accessible arteries The details have been described by Lexter<sup>26</sup> By this method a rather crude imitation of chronic albuminuria was achieved, with the advantage of avoiding any direct damage to the kidneys The animals were on the usual stock diet unrestricted as to water and given daily about 1500 cc of 0.85 per cent sodium chloride solution by stomach tube to ensure an adequate supply of the elements of edema fluid Analyses of the blood and the transudates were carried out by means of standard chemical procedures Material from organs or tissues at autopsy was worked up in the usual histological manner



Fig 1 Dog 11 in recumbent position to show the edematous abdominal wall and the swelling of the thighs

**The Results** Low Plasma Proteins and Edema in Dogs — Adequate plasma depletion requiring the daily bleeding of 10 kg dogs to the extent of 500 to 1000 cc promptly leads to a progressive fall in the concentration of the plasma proteins so that usually within three or four days values of about 3 per cent are obtained representing about one-half of the normal concentration in dogs At this point if plasma depletion is still continued in order to offset the rapid regeneration of the plasma proteins edema makes its appearance and increases progressively This is shown simultaneously in the rising weight curve gains of 10 to 30 per cent often occurring within a few days to be followed by equally striking drops in weight when edema disappears The extent of edema depends on many factors but chiefly upon the possibility of maintaining the plasma protein level below the critical concentration This varies with the individual dog However no exception has been found to the rule that edema always appears in the dog whenever the plasma

proteins have been reduced to about 50 per cent of their normal value and kept at or below this level. Should plasma depletion be discontinued for one or two days a sufficient rise in the plasma protein concentration occurs to bring it above the edema level and the process shifts in the direction of rapid diuresis and complete disappearance of edema. This reversible reaction has been observed with great regularity. The change from a state of edema to one of no edema occurs so rapidly with the elimination of only one factor, plasma depletion that a cause and effect relationship between reduced plasma proteins and impaired reabsorption of fluid from the tissue spaces can scarcely be questioned. Edema has been produced in varying degrees in about 40 dogs. Figs. 124, 125 and 126 illustrate the sequence of events in these experiments.

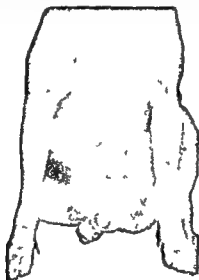


FIG. 123 — Marked edema of the abdominal wall and external genitalia also ascites in Dog 11.

**Distribution of Edema** —The edema is first noticeable in the soft tissues about the inner aspect of the thighs, the external genitalia and the inguinal region. It pits readily and can easily be squeezed from one subcutaneous area to another. As the edema increases, the buttocks and perineal region become more swollen, the posterior aspect of the thighs down to the knees is involved and the hind legs become rounded out. The abdominal wall becomes definitely edematous at first in the suprapubic and lower lateral regions, later all the way up to the costal margin. In extreme cases the anterior

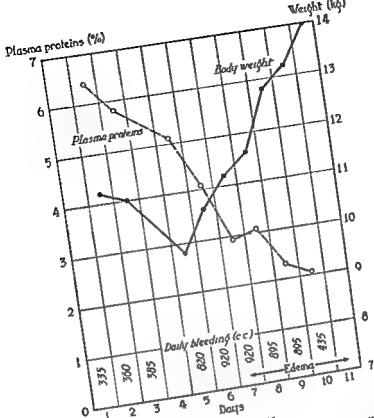


FIG. 124 — Dog 11

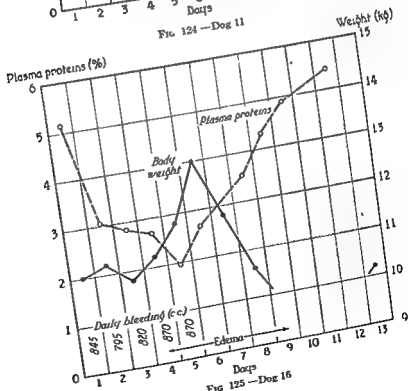


FIG. 125 — Dog 16

and lateral chest walls are also involved and occasionally the neck develops rolls of edematous tissue. The forelimbs are usually unaffected. Ascites usually makes its appearance early, may increase to 1000 cc. or more and be associated with respiratory embarrassment. Hydrothorax and pulmonary edema have been observed in extreme instances and have at times been the immediate cause of death.

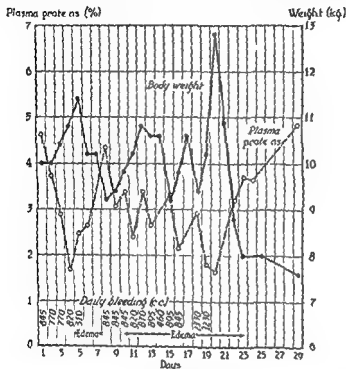


FIG. 126—Dog 17

The subcutaneous edema fluid is always freely movable in the tissue spaces and responds readily to changes in the position of the animal. When the dog is tied down on his back the swelling rapidly accumulates on the sides of the neck and the forelimbs. The fluid is always freely movable in the tissue spaces and responds readily to changes in the position of the animal. When the dog is tied down on his back the swelling rapidly accumulates on the sides of the neck and the forelimbs. The fluid is always freely movable in the tissue spaces and responds readily to changes in the position of the animal. When the dog is tied down on his back the swelling rapidly accumulates on the sides of the neck and the forelimbs.

Distribution of the excess fluid in the tissues is closely analogous to that seen in human anasarca. The loose areolar layers in the subcutaneous tissues are filled out with a clear or slightly opalescent fluid which also extends into the intermuscular planes and into the connective tissue septa between the muscle bundles. The greatest amount of fluid is found between the upper dermis and the muscular level. The peritoneal and retroperitoneal tissues are infiltrated

section of edematous abdominal wall illustrating the typical separation of collagen bundles by the accumulation of a large amount of intercellular fluid

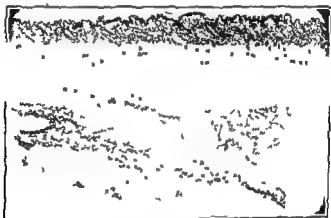


FIG. 127. Typical edema of the skin and subcutaneous tissues of the anterior abdominal wall of Dog 10. Low magnification.

There is little question as to the free nature of the edema fluid even early in its development. Needle punctures or other injuries to the skin overlying an edematous area lead to constant oozing or

simple matter. When obtained without any admixture with blood the subcutaneous fluid is colorless, water clear or slightly opalescent. Ascitic fluid is more likely to be opalescent.

**Low Protein Content of the Experimental Transudates.**—The composition of this experimental transudate is of the greatest importance insofar as it concerns the protein content. In regard

the significance of Starling's insistence upon the distinction between the fluid in the potential tissue spaces and lymph as collected from some duct. True tissue fluid cannot be obtained analytically, but the striking difference in the protein content of lymph from different regions of the body indicates that there is a difference in the permeability of the capillaries for the plasma proteins. Since the peripheral capillaries in contrast to those of the abdominal viscera are the most impermeable to protein under normal conditions, edema fluid formed in the periphery should have a very low, or negligible protein content provided that no injury of the capillary endothelium exists to alter the normal impermeability. The high protein content of most of the experimental edemas reviewed earlier in this chapter is due to direct damage of the capillary walls by what are known as vascular poisons. These edemas might be considered as exudates rather than transudates. Nephrotic edema is simply an ultrafiltrate of the plasma theoretically dependent on a disturbance in the equilibrium of the physical forces controlling the water balance between the blood and tissue spaces and independent of hypothetical changes in the permeability of the capillaries to salt and water since the latter pass freely in both directions at all times. The criterion for the nephrotic nature of an experimental edema is the low concentration of protein in the edema fluid.

FIG. 43.—THE LOW PROTEIN CONTENT OF EXPERIMENTAL NEPHROTIC EDEMA IN DOGS (LEITER<sup>10</sup>)

Dog	Edema fluid	Protein per cent
10	Ascitic	0.04
	Ascitic	0.12*
11	Ascitic	0.08
	Ascitic	0.47
	Ascitic	0.4
11	Subcutaneous	0.20
	Ascitic	0.4
15	Ascitic	0.35
	Ascitic	0.0
	Subcutaneous	0.0
16	Ascitic	0.30*
	Ascitic	0.11*
	Subcutaneous	0.0*
17	Subcutaneous	0.04*
	Subcutaneous	0.0
	Ascitic	0.15
3	Ascitic	0.04
	Subcutaneous	0.01
	Ascitic	0.04
33	Ascitic	0.11
	Subcutaneous	0.04
47	Ascitic	0.07
	Ascitic	0.09
41	Ascitic	0.12
	Ascitic	0.01*
50	Ascitic	0.10*
	Ascitic	0.10*

\* Only the total nitrogen was estimated on the edema fluid. The plasma non-protein nitrogen value was used in calculating the protein content.

## EXPERIMENTAL NEPHROTIC EDEMA

The chemical analyses of subcutaneous and ascitic transudates have given gratifying results. Table S3 shows the figures for the earlier experiments. All but one of the values for the protein content of subcutaneous edema fluid fall below 0.1 per cent while those for ascitic fluid are usually below 0.3 per cent. It is interesting that many values fall within the range for the protein content of cerebrospinal fluid considered by many investigators as an ultrafiltrate of the plasma. These figures compare favorably with those shown in Table S8 for clinical nephrotic edema. It seems that these analyses establish for the first time the production of nephrotic edema in an experimental animal.

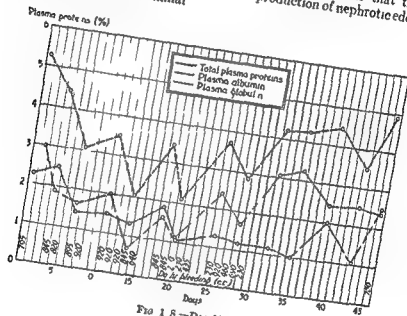


FIG 18 - Dog 90

### Regeneration of Plasma Albumin and Globulin During Plasma Depletion

During the course of these experiments one could not help being struck by the capacity of the dogs to regenerate their plasma proteins. Kerr, Hurwitz and Whipple<sup>11,12</sup> have worked out very thoroughly the conditions for regeneration following acute depletion of plasma proteins in dogs but their method of plasma pheresis did not give them the opportunity of carrying on chronic experiments. The persistent reversal of the albumin

plasma of not  
known  
globulin  
fractions

and to follow the course of these  
periods of prolonged plasmapheresis interspersed

with periods of remission. The results are illustrated in Fig. 128. It is obvious that while at first the curves for total protein, albumin and globulin parallel each other, later there is a sharp separation so that with each respite from plasma depletion the total protein and globulin curves rise sharply but the albumin curve lags behind and tends to remain flat over long periods. It seems as if the regeneration of plasma globulin is a rapid process while albumin is more slowly formed. Hence the  $\frac{\text{albumin}}{\text{globulin}}$  ratio remains low for some time.

The tendency to edema is determined not by any specific albumin or globulin level but rather by such a combination of the two that the total plasma protein osmotic pressure is less than the value necessary to prevent an excess of filtration over reabsorption of fluid in the capillaries.

When plasma depletion has continued for weeks or months the animal is likely to become emaciated even in the absence of infection.

served of failure to increase the plasma globulin as soon as depletion was temporarily discontinued regardless of the state of nutrition of the animal. Considerable time may be required however for complete restoration to the normal level.

**Changes in Blood Cholesterol During Plasmapheresis**—The blood cholesterol was followed in many experiments in order to determine whether there was any analogy with the condition occurring in nephrotic glomerulonephritis and nephrosis. Some investigators believe that the high blood-cholesterol level in active nephrotic renal disease is somehow related or secondary to the decrease in the plasma proteins.<sup>16</sup> Others think that it represents a primary disturbance. All admit that the blood cholesterol is characteristically and persistently elevated in nephrotic renal disease. Recently Barker and Kirk<sup>2</sup> stated that the blood cholesterol in dogs undergoing plasmapheresis becomes elevated thereby producing a picture

associated with prolonged undernutrition or inanition in man and tends to rise only with improved nutrition.

The results fall into two main groups as reported previously.<sup>40</sup> First there are the experiments of short duration, say less than two weeks, in which plasma depletion is associated with either a fall or at times a considerable rise in blood cholesterol, unpredictable and



varying from dog to dog. In the second place come the longer experiments in which, after the first irregularities the blood-cholesterol curve seems to follow a rather definite cycle, tending to

as plasma depletion begins anew

Any attempt to explain the blood-cholesterol curves in the dogs at present is purely speculative, since little is known as yet about fat metabolism under varying conditions. The situation in nephrosis in man has been reviewed by Leiter,<sup>42</sup> who pointed out some of the more obvious defects in the knowledge of this problem. If one may speculate, it would seem that the marked fluctuations occurring in the blood cholesterol during short depletion experiments may represent a resultant of such factors as the washing out of plasma cholesterol, the mobilization of cholesterol with the fats from the fat depots and its transport in the circulation, and alimentary hypercholesterolemia, to mention only the more important ones. On the other hand, in the long experiments each period of plasma depletion is associated with a considerable loss of blood cholesterol while, in the interim between bleedings, the supply of endogenous and exogenous cholesterol to the blood is perhaps not as rapidly taken care of by the liver of the undernourished animal as normally. Hence the blood cholesterol rises sharply and remains elevated until equilibrium between supply, transport and removal is reestablished. This is only a working hypothesis and requires confirmation by further experiments. The hypercholesterolemia produced in rabbits by frequent bleeding as reported by Fishberg and Fishberg<sup>43</sup> is apparently a process quite different from the situation in the dogs during plasmapheresis.

#### THE RELATION BETWEEN THE EXPERIMENTAL AND CLINICAL NEPHROTIC EDEMAS

**The Experimental Edema as a Pure Nephrotic Type** — From the review of the clinical nephrotic edemas and the consideration of the previous forms of experimental edema it seems fair to conclude that the edema just described may be classified as a nephrotic type. It represents a rather pure form of nephrotic edema in comparison to that seen in nephrotic glomerulonephritis, because in the latter there occur transitions between nephritic and nephrotic edemas making interpretation at times difficult. The experimental dropsy in the dog has been shown not to be cardiac in origin<sup>44</sup> and is unrelated to renal function or pathology, although the kidney may show various lesions directly or indirectly connected with the

experimental procedures used. Vascular damage is ruled out by the composition of the edema fluid. In short, the factors assumed to be responsible for the experimental edemas previously described, with the exception of the nutritional edemas in rats, are here absent or unimportant. The theory of Starling, as elaborated by Epstein,

at first glance so unrelated to one another.

**Experimental Nephrotic Edema in Dogs is not Nephrosis**—It seems probable that all that has been produced is a disturbance in

than edema to make any one of these states, although edema may be the outstanding feature. To produce real experimental nephrosis, there must be present the characteristic disturbances in lipid metabolism: the cholesterol-ester infiltration of the renal tubular epithelium, the doubly refractile lipid droplets in the urine, to mention only the most obvious findings in clinical nephrosis. Such a picture has never been produced. The author has examined many

except occasionally at the borders of and in organizing infarcts. The blood-cholesterol curves have already been described and the lack of resemblance to human nephrosis seems clear. It must be agreed upon that the experimental edema in dogs is nephrotic but not nephrosis.

**The Time Factor in Nephrotic Edemas**—The edema in dogs is produced too rapidly, a matter of a few days, to be entirely analogous with the nutritional edemas of man and those observed in rats and other animals. The factor of time, however, must not be forgotten. Where undernutrition is a gradual process, there is ample time for readjustment and the human body can carry out a conservation of protein in the blood.

or protein builders in diarrheal stools. In patients with active nephrotic renal disease, the continual albuminuria is the serious occurrence. Yet the human body can regenerate plasma proteins fairly well, since a nephrotic patient may maintain a constant plasma protein level for months in spite of the loss of 10 gm. of protein per day. A 10-kg. dog often does better than that. In the dog experiments there is little time for adaptation; the physical

mechanism for maintaining the water balance is taken by surprise and edema can be produced long before any emaciation has occurred. This seems to indicate that emaciation *per se* is not a *sine qua non* for nutritional edema. The prompt response to proper therapeutic measures in the clinical cases indicates the subsidiary rôle of loss of body weight.

### THERAPEUTIC PROBLEMS AND PRINCIPLES

#### Problems of Therapy in the Nephrotic Edema of Man and Dog —

Clinical nephrotic edema is a chronic process when found in association with renal disease because the fact that albuminuria has persisted long enough to reduce significantly the plasma protein level makes a sudden cessation or decrease in albuminuria unlikely. In these patients restriction of salt and fluid in the diet may have little effect upon an existing edema if it is extensive. The problem then is how to stimulate more rapid formation of plasma proteins in order to overbalance the loss in the urine.

The dog with experimental nephrotic edema at first is unable to restore plasma protein as rapidly as it is being removed but within a few days the supply almost equals the demand. When plasma pheresis then is discontinued for only twenty four or forty-eight hours the stimulus to regenerate the proteins is effective enough to raise their concentration in the plasma above the edema level. Marked diuresis sets in and edema disappears rapidly, in spite of the continued administration of large amounts of isotonic salt solution by stomach tube. In the dog therefore we are dealing with an acute easily reversible nephrotic edema that requires no treatment other than to check the drain upon the plasma proteins.

The non albuminuric nutritional nephrotic edemas observed clinically form a sort of combination of chronic and acute insults the chronic damage being represented by a long period of gradual emaciation and a slow fall in the plasma proteins the acute being manifested often in a temporary severe diarrhea or some infection followed by a period of relatively huge intake of salted fluids such as soups to appease the urge for food. The edema appears shortly thereafter and may or may not spread rapidly. The relatively simple procedure of rest in bed and restriction of salt and water may be highly effective in bringing about the disappearance of edema provided the plasma proteins are not too low. When these are very much reduced edema may not decrease in spite of the limitation of water and salt. Just how low this protein level must be is not known at present. It is in this non albuminuric group that blood or plasma transfusion would seem to be the most hopeful measure for rapidly raising the plasma proteins above the critical

edema level. A successful instance of this therapy was recently reported by Landis and Leopold.<sup>28</sup>

**Principles of Therapy in Nephrotic Bright's Disease**—The principles of therapy in what are to clinicians the most important and the most difficult cases of nephrotic edema, that is in nephrotic Bright's disease, may be derived from further consideration of the relation between experimental nephrotic edema and the clinical forms. In both animals and man the capacity for regeneration of the plasma proteins is almost unlimited. The human being, however, sooner or later acquires a distaste for food for diverse reasons or acquires what is worse, wrong suggestions and advice concerning  
 less  
 what  
 letion  
 rate

Until recently patients with nephrotic Bright's disease were treated

better to make certain first of an optimal rather than a minimal protein intake, second of an appetizing variety of foods to make possible a high caloric diet necessary to overcome the existing undernutrition masked by the edema, and third of a limitation of salt and fluids insofar as it is consistent with the adequate consumption of food. Furthermore, with protein continually being lost in the urine, it would seem inadvisable to remove by paracentesis collections of even a low protein ascitic or other transudate. The total amount of plasma protein discarded in this manner becomes quite significant. Conservatism is therefore indicated unless the patient's condition warrants rapid action. The nephrotic patient is ordinarily not treated sufficiently, while his edema is given too much treatment. In a condition that takes considerable time to develop, sufficient time must be allowed for dietary or other measures to work. Under conditions not understood at present, even the albuminuria may diminish to a point where it is no longer a serious loss of protein. The plasma proteins then increase above the edema level, although the rate of this process in relation to the degree of albuminuria is practically unknown. Edema disappears and the patient may be in apparently good health for a

another, they have been stressed repeatedly in the last thirty years. They still need repetition in view of the prevailing confusion in the practice of the healing art in this branch of medicine.

## ADDENDUM

Since this chapter was written considerable evidence has accumulated in the literature confirmatory of the basic conceptions of nephrotic edema. In regard to clinical nephrotic edema the predominating role of undernutrition or loss of plasma protein from the body by various routes has been firmly established by the studies of many investigators<sup>74, 8, 28, 33, 39, 9</sup>. The importance of their findings in stimulating rational dietary therapy cannot be overemphasized.

Experimental nutritional nephrotic edema has been produced in the dog by Shelburne and Fglhoff<sup>90</sup> using a diet low in protein but adequate in other respects. There was a close analogy between this nutritional edema and plasmapheretic edema. Weech Snelling and Goettsch<sup>9</sup> have made a more extensive study with these two methods of producing nephrotic edema in dogs and have stressed the significance of the plasma albumin level in relation to the appearance of edema. The low protein content of experimental nephrotic edema fluid was confirmed by these investigators. Bloomfield<sup>76, 78</sup> has reopened the problem of carrot edema in the rat by failing to produce low serum proteins or edema in mature rats on low protein diets not containing carrots.

Plasmapheretic edema in dogs has been reproduced by many investigators. Darrow Hopper and Cary<sup>77, 78</sup> made careful studies of the electrolyte pattern of the serum and ascitic fluids in their edematous dogs. Lepore<sup>84</sup> investigated the distribution of chloride and water in various tissues and organs. Fahr and his associates<sup>79</sup> emphasized the salt factor in experimental edema. Kumpf<sup>81</sup> bled

The quantitative relationships between venous plasma colloid osmotic pressure of the blood and rate of filtration of fluid through the capillary wall in normal human subjects have been determined by Krogh Landis and Turner<sup>8</sup>. Their results are in full accord with the Starling Krogh Epstein theory of nephrotic edema as a quantitative disturbance in the normal mechanism of fluid balance. Loeb and his associates<sup>87</sup> arrived at a similar conclusion after a study of normal individuals and a study of the effect of Cl and NaCl

in the regeneration of plasma protein has recently been attained in an ingenious manner by Holman Mahoney and Whipple<sup>88, 81</sup> who have calculated the amount of new plasma protein formed in the dog under standard conditions in response to various dietary proteins. Further development of this line of investigation may have far reaching effects upon the treatment of clinical nephrotic edema.

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## CHAPTER XXVI

### EXPERIMENTAL EDEMA THE EFFECT OF LOW PLASMA-PROTEIN LEVEL UPON WATER BALANCE AS RELATED TO SPECIFIC IONS \*

By M. HERBERT BARKER M.S. M.D.

**Introduction**—In 1827 Bright\* pointed out the relationship

ciency affected chiefly the albumin causing the ratio of the albumin to globulin to fall below unity. Epstein<sup>20, 1</sup> found low proteinemia to be characteristic of those cases of chronic parenchymatous nephritis called nephrosis by Muller<sup>21</sup> Munk<sup>22</sup> and Volhard and Fahr<sup>23</sup>. Epstein<sup>2</sup> considered the low protein level to be the result of the marked albuminuria and that it so reduced the colloid osmotic pressure that seepage of fluid into the tissues took place thereby causing the edema. He suggested the feeding of a high protein diet to patients presenting albuminuria, edema and low serum protein. This regime brings about remarkable improvement in some cases with disappearance of edema and return of the blood proteins to normal levels while in other cases it has been of no demonstrable help. Other factors such as elimination of infected foci, bed rest, restriction of salt or the giving of various substances such as ammonium chloride, calcium chloride, ammonium nitrate, urea, thyroid extract, pituitary extract, hypertonic glucose and salyrgan have each at times apparently relieved edema after other means have failed.

The appearance or disappearance of edema does not follow the plasma protein concentration as might be expected. Under Lundgaard and Van Slyke<sup>24</sup> did not find any close relationship between variations in edema and the plasma proteins although they felt certain that the albuminuria was an important factor in reducing the concentration of the plasma proteins. The majority of their patients with small urines exceeding 1 gm. per day showed a reduction in the total protein and in the ratio of albumin to

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## EXPERIMENTAL EDEMA

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globulin. These authors concluded with Epstein<sup>22</sup> that the clinical picture was an expression of an underlying metabolic disorder of a fundamental nature.

The importance of the level of the plasma proteins in relation to nephrotic edema has been experimentally demonstrated by Leiter<sup>23</sup> and Barker and Kirk.<sup>24</sup> These workers have produced nephrotic edema in dogs by the reduction of the plasma proteins by repeated plasmapheresis.<sup>25</sup> Their experiments support the original hypothesis of Epstein.<sup>21</sup>

The process of removing large amounts of blood with the reinfusion of the cells after discarding the plasma is regarded as an adequate substitute for proteinuria. If this process can be carried out over long periods of time chronic nephrotic edema so produced can be studied in detail under relatively well controlled conditions such a study might be of help in interpreting clinical findings and suggesting therapeutic measures. With this idea in mind an attempt has been made to ascertain more about the factors that influence the edema associated with low proteinemia.

**Method.** Six young adult dogs weighing 15 to 20 kg. were selected and placed in metabolism cages. They were fed liberally an adequate diet as given to dogs in the Department of Physiology at Northwestern University, Chicago III. This diet was maintained nearly constant. It included about 12 gm. of sodium chloride and 500 to 800 cc. of fluid daily. The dogs were given water *ad libitum* and the fluid intake and urinary output were recorded for twenty-four hour periods together with the body weight. Two dogs were kept as controls while 4 were so trained during the preliminary observation periods that all procedures could be carried out without the use of sedatives or anesthetics. Low proteinemia was produced and maintained by plasmapheresis. The dogs were bled the proper amounts which varied for each animal.

The bleeding was accomplished by direct puncture of the femoral artery with a No. 19 medium bevel needle. As soon as the flow was established the needle was connected to a firm rubber tubing 15 inches long and attached to a right angle glass tube placed through a 2 hole rubber stopper and reaching nearly to the bottom of a 250-cc. centrifuge bottle containing 15 cc. of 10 per cent sodium citrate solution. A short glass tube was placed in the oil or hole of the stopper and connected to a long piece of heavy rubber tubing. This was connected to an air-suction apparatus so that moderate negative pressure could be maintained within the centrifuge bottle to facilitate bleeding. With this method the removal of 500 to 1000 cc. of blood could be accomplished by merely changing the stopper from one centrifuge bottle to another without clotting taking place in the needle. Care was exercised to agitate the centrifuge bottle gently during the bleeding.

The bottles were covered with rubber caps and centrifuged at 1000 r p m for twenty minutes. The plasma was removed by suction through a small sterile glass pipette. The red cells were diluted to their original volume.

with Ringer's solution. Another two hole stopper with its glass and

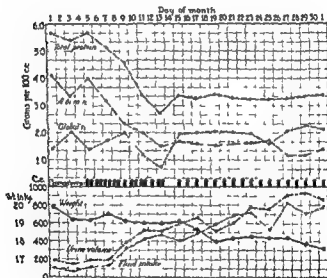


Fig. 329. Illustrating how the levels of the serum proteins the water intake and

increase of urinary output

**Results.**—The daily removal of 750 cc of blood with reinfusion of the cells after discarding the plasma resulted in a rather rapid lowering of the serum proteins. If plasmapheresis was carried out

two or three times daily, the depression of the proteins was more quickly brought about. This was shown by Dog 6 (Fig 129). When the serum proteins were reduced to about 3.5 per cent slight pitting edema of the legs, scrotum and abdominal wall appeared. In general this soft dependent edema increased if the vigorous bleedings were continued and disappeared within a few days following the cessation of bleeding.

The first and important part of the problem was to produce a slight and constant edematous state as the basis for the study. This condition was brought about by daily plasmapheresis in varying amounts until the proper volume was found necessary just to maintain the animals with slight pitting edema of the legs. This was accomplished with difficulty in some animals and with ease in others. As an example of the former Dog 3 required the removal of 38,000 cc of blood over a period of two months in order to produce a state of edema that could be regarded as constant. After this time he was easily held on the edema margin by removal of 500 cc about four times a week. As an example of the latter the total serum proteins of Dog C were reduced from their initial level of 6.3 gm to about 3.3 gm per 100 cc in a period of ten days by plasmapheresis of 8000 cc. After this time slight edema was present. The edema and the serum protein level of about 3.3 gm were maintained quite constant by the daily removal of 450 to 475 cc of blood (Fig 129). This volume seemed to correspond to the amount of protein this particular dog could regenerate per day.\*

The level of the water balance showed marked changes during the period of protein depletion and during the period of edema maintenance. There was a gradual increase of thirst as the serum proteins were reduced. The animal frequently showed an increase of 500 to 800 per cent in the water drunk. Urine volume increased in the same proportion and there was no water retention until the serum proteins were further depressed (Fig 129). No explanation for this elevation of the level of water metabolism is evident. Dog 3 showed the greatest increase of volume intake. He drank between 900 and 1100 cc per day during the control period and during the

\* The rate of globulin was very rapid as compared with albumin so that the

period when edema was maintained his intake and output gradually increased to 4500 or 5500 cc per day without any remarkable variation in weight dict before the the serum prot 800 cc per day

he had been carried under good control for the longest period of

were on the whole about 1.5 per cent each and the urinary output of 4500 cc was essentially the same from day to day (Fig. 130, lower graph). The average weight was about 19.5 kg and the chloride intake (the food contained about 1.3 gm NaCl daily) and the chloride excretion ran quite parallel (Fig. 130 middle graph).

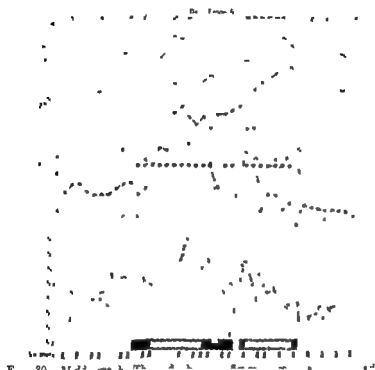
Sixteen gm of sodium chloride were then added daily to the water drunk by the dog. Water and chloride retention immediately began and the body weight increased 53 per cent in five days. By this time edema and ascites\* were massive and the animal was able to get around only with difficulty. Plasmapheresis was discontinued for three days and soon the chloride output began to

urine volume the led on three suc- the chloride and urine excretion and the body weight rapidly increased to the previous level. This sharp response of water and chloride excretion (Fig. 130 middle graph fifteenth, sixteenth and seventeenth days) following the cessation of plasmapheresis (twelfth, thirteenth and fourteenth days) together with the equally marked reversal of the salt and water balance following the renewal of the bleedings (seventeenth, eighteenth and nineteenth days) demonstrate the importance of the level of the serum proteins in this type of edema.

Potassium chloride was then substituted for sodium chloride. Sixteen gm of the potassium salt were added to the water which the dog drank readily. Within a few hours an increase of the urinary output was evident. A marked diuresis followed which caused

\* The ascitic fluid had a protein content of 0.10 to 0.11 per cent which seemed to consist entirely of albumin. The chlorides were 30 to 740 mg per 100 cc and the freezing point was  $-0.51^{\circ}\text{C}$ .

all the ascites and edema to disappear within three days. The body weight dropped 5.5 kg. in twelve hours and continued to fall



#### loss of the edema

until it reached a level below that of the foreperiod. The dog showed an increased desire for water while the sodium chloride was given. His intake gradually rose until he drank 9000 cc. during

one day. This huge intake occurred while he was retaining large amounts of salt and water (Fig 130). The fluid intake was well above the urinary output during this period. As soon as the potassium salt was substituted for the sodium there was an apparent saturation of the thirst and the fluid intake quickly fell below that of the foreperiod. The urinary output exceeded the intake by 500 to 2,000 cc per day. The chloride excretion rose sharply as the potassium salt was started but soon the calculated intake of chloride and the chloride excretion were about equal. The chloride intake and output thus remained in equilibrium on a high level until the potassium chloride was discontinued following which the chloride

protein was below that determined at any previous time. The

normally about 550 mg per 100 cc began to fluctuate and soon increased to about 640 mg (Fig 131). This increase was associated with chloride retention and the formation of edema as described

mg point of the serum showed a sudden depression coincident with the feeding of the sodium chloride. There were some rather wide fluctuations in the freezing point readings but the average trend was downward (Fig 131). The control determinations were  $-0.55$  to  $-0.56^{\circ}\text{C}$  with gradual increase to  $-0.63^{\circ}\text{C}$ . As soon as the potassium chloride was started the freezing point gradually returned toward the normal. It rose from  $-0.63^{\circ}$  to  $-0.573^{\circ}\text{C}$  in eight days. Rather wide variations in the freezing point readings were obtained while sodium chloride was given. The lowest value reached by the freezing point was  $-0.19^{\circ}\text{C}$ . This determination is rather far removed from the average readings but check determinations gave identical results. This low freezing point was obtained while the greatest retention of water took place. On the



whole there was no close correlation but the freezing point curve seemed to follow that of the body weight (Compare Figs 130 and 131). As edema decreased, the freezing point rose. The

freezing-point being nearest to normal when the blood chlorides were at their height \*

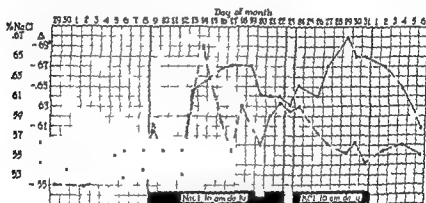


Figure 131. Freezing point of the blood chlorides during the feeding of

The hydrogen-ion concentration of the blood showed considerable variation. During the period of sodium chloride administration there was a gradual fall of the pH from 7.29 to as low as 7.13.

the pH were not obtained during the control periods or after the salts were discontinued. Although the results were not clear-cut, the hydrogen-ion concentration as determined was on the average, much increased during the period of chloride administration. The

\* Some of the discrepancies encountered between the different terminations are due to the lack of parallelism between

carbon dioxide combining power of the blood showed a rather sharp increase from 41 to 52 volumes per cent seven days after starting the sodium chloride. This elevation of the blood  $\text{CO}_2$  continued until five or six days after the potassium chloride had been discontinued. On the whole, the blood pH was decreased and the blood  $\text{CO}_2$  was increased (Fig. 13). No explanation was apparent for the late return of the carbon dioxide to its normal level.

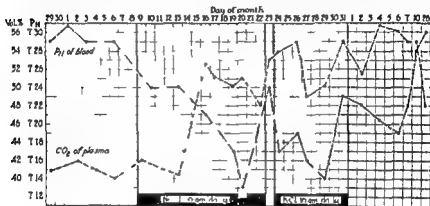


FIG. 13. Illustrates the blood pH and the plasma  $\text{CO}_2$  changes during the period shown in the preceding figures. There was an average increase of the blood pH and a marked increase of the blood  $\text{CO}_2$  combining power. Note the gradual elevation and delayed fall of the  $\text{CO}_2$ .

**Discussion.** The studies by Leiter and by Barker and Kirk have offered the experimental proof for Ispat's theory for edema as due to hypoproteinemias. Since Ispat's theory was proposed more attention than earlier has been given to the pathogenetic differentiation of clinical edema. The nephrotic edema for which Ispat's theory applies is differentiated at least on the American continent from the edema of acute nephritis. The earlier theories concerned themselves with the common edema of subacute and chronic nephritis. All the patients on whom the mechanism of edema was studied in the more important papers before Ispat

figura as leading symptom and based its explanation of edema upon the concept of hydremic plethora (Grainger-Stewart<sup>22</sup> and Bartels<sup>23</sup>). Failure through huge intravascular injections experimentally to produce a water retention resembling the edema in Bright's disease demonstrated the insufficiency of this concept and

led Cohnheim and Lichtheim to assume an alteration in vascular permeability as the significant factor in nephritic edema (1877). Today Volhard on the whole adheres to this theory, the same concept likewise forms a part of the theory of Achard.

Though Hamburger<sup>1</sup> deserves the credit as the first to have called attention to the avidity with which a constant osmotic pressure is preserved in the body, it was through the work of Koranyi in the late 90's that this idea became fruitful to clinical medicine and

workers Lemierre and Javal<sup>40,41</sup> when in their well known clinical experiment through the administration or withdrawal of sodium chloride they caused nephritic edema to augment or diminish as the chloride balance shifted between positive and negative according to the phase of the experiment. Similar experiments with identical results at about the same time were carried out in Koranyi's Clinic by Kovesi and Róth-Schulz.

Seeing in the NaCl retention the chief cause of the edema, Vidal ascribed the retention to an inability on the part of the kidney to eliminate the salt, while Achard assumes an alteration of the tissues as the cause of the salt retention and the edema.

Attention might be called to two points in the experiments from this period. In 2 patients, 1 of Vidal and Lemierre and 1 of Courmont, the addition of sodium chloride to the diet besides increasing the edema, also precipitated attacks of convulsive uremia. The second point. Neither in the experiments of Vidal nor of Kovesi and Róth-Schulz was there any parallelism between NaCl retention and weight gain, the gain in weight falling far behind the retention as measured by the determination of the chlorides and calculated either as a solution of the chloride content of the plasma or of the concentration of a physiological saline solution.

The occurrence of considerable edema in diabetic patients to whom large amounts of NaHCO<sub>3</sub> were given together with observations that in hydropic nephritics bicarbonate like NaCl will increase the edema (Blum), as is also the case in patients afflicted with hunger edema (Hulse, Berglund), are all well known observations indicating the importance of the Na ion rather than the Cl ion.

Hastings and Van Dyck through their discovery of the bromide edema and the demonstration of the complicated nature of its mechanism were able to shift the interest back to the importance of the anions.

Bunge remembered for his discussion of the diverging dietary habits in the world's population, especially in regard to the use of sodium and potassium, was the first to demonstrate (1873) in careful experiments that ingestion of small amounts of potassium salts

might cause the elimination of considerable amounts of sodium chloride. The proven diuretic action of various potassium salts (Bock Adolph) by Fichholtz and Starling<sup>13</sup> has been coupled with the simultaneous presence of excess of calcium, the mechanism for the effective combination of these two cations remain unexplained.

Gamble as well as McQuarrie have correlated the potassium content of the cells and sodium content of the extracellular fluid with the urinary excretion of the same cations for the purpose of analyzing the origin of lost water in controlled experiments. To summarize the composition of the fixed base under different conditions is assuming a position in pathology of increasing importance.

Volhard in 1914 introduced the useful term *Oedembereitschaft* an expression which with a slight shift in meaning usually is rendered as tendency to edema.

The experiment reported in this chapter on the basis of Epstein's theory and the experimental proof for the same rendered by Lister and by Barker and Kirk in its long foreperiod offers one possible correspondence to the clinical stage of *Oedembereitschaft*. In its NaCl feeding experiment it leads us back to the observations of the time of Widál but on the new basis of hypoproteinemia. In its KCl experiment it again centers the interest upon the cations.

**Summary** A method for the production and the maintenance of a nephrotic type of edema is described. An increased thirst was associated with reduced serum proteins but there was no retention of water in the tissues until the serum proteins were reduced to 3 or 3.5 per cent. Factors that influence water balance may be successful.

type of  
edematous  
reduced serum  
sodium chloride  
water balance  
has been of  
their edema. These experiments further point toward the importance of the sodium ion as a factor of significance in the formation of edema. More rigid dietary control of edematous patients reducing the sodium and increasing the potassium intake is indicated. The chlorine ions play a less important role. It is suggested that in nephrotic edema the restriction of water probably will not greatly influence the underlying cause of the edema. It appears that the increase of the serum protein and the restriction of the sodium ion are the factors of greatest importance in the control of nephrotic edema.

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## PART V

# OCULAR CHANGES IN BRIGHT'S DISEASE

### CHAPTER XXXVII

#### RETINAL LESIONS IN NEPHRITIS AND HYPERTENSION

By HENRY P. WAGENER, M.D.

#### RETINITIS IN NEPHRITIS

Lesions in the retina in cases of nephritis vary considerably in type and their exact relationship to the general features of the disease is often not obvious. In the main when retinitis is present definite retention of urea will be found. But retinitis does not always accompany renal insufficiency and apparently it has no direct relationship to the presence or the degree of retention of urea.

**nephritis:** Lesions in the retina are rare in the other varieties of nephritis. (From the retinal standpoint the arteriosclerotic kidney is considered as a part of the picture of essential hypertension.)

In cases of *nephrosis* retinitis is never seen. Occasionally in the presence of marked generalized edema slight edema of the retina may be suspected but the author has never seen it sufficient in degree to justify a definite diagnosis. The retinal vessels are always normal in pure nephrosis. The development of arteriosclerosis should always suggest that an evolution of the nephrosis into glomerulonephritis has taken place. In cases of nephrosis in which there is an increased concentration of blood fats the blood in the retinal vessels may have a slightly creamy tint. But this *lipemia retinalis* is always mild and transitory.

In *focal nephritis* the fundus is normal. In cases of *ascending pyelonephritis* of severe grade occasional usually single hemorrhages or cotton wool patches may be found in the retina. But these may be seen in general toxemia or septicemia from any source and are not characteristic of the renal disease and are not related to the degree of renal insufficiency.

Sclerosis of the retinal arterioles is seen at times in association with *polycystic kidneys*. This sclerosis is of the usual type seen in essential hypertension and when retinitis occurs it is not distinguished from the retinitis of severe essential hypertension. It is ret

initis of hypertensive disease and not retinitis of nephritis although the hypertension probably arises as a sequel to the renal lesion.

*Glomerulonephritis* is the only variety of nephritis in which retinitis is at all common. The retinitis of chronic glomerulonephritis commonly designated "albuminuric retinitis" is characterized by anemia and edema of the disk, generalized usually rather dense grayish white edema of the retina, visible especially for 3 or 4 disk diameters around the disk (snow bank exudate), hemorrhages and occasional cotton wool patches superimposed on the edematous retina and in the macular region the radiating star figure made up of rather large thick groups of irregularly shaped hard white

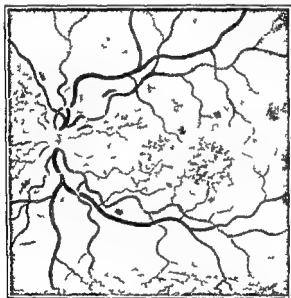


FIG. 133. Retinitis of chronic glomerulonephritis.

exudate. The vessels, especially the arterioles, are difficult to distinguish because of the surrounding edema, but they often appear narrowed and sclerosed (Fig. 133).

The picture which is the one usually given is really that of a late stage of the retinitis. In the most typical cases the outstanding feature of the early stage is generalized edema of the retina. Vascular changes are not striking. There is likely to be generalized constriction of the arterioles, but no definite sclerosis. The edema fluid is at first of watery consistency and its presence is difficult to recognize except through blurring of details. A few flame-shaped hemorrhages are usually scattered through the retina. The edema gradually becomes more extensive and the fluid of denser



albuminous appearance. It is often sufficient in amount to cause detachment of the retina. The spots arranged around the macula as the 'macular star' are formed in the process of absorption of the edema fluid and therefore indicate that the edema is receding. They are not characteristic of nephritis but are found in edema from any cause if the edema involves the macular region. In less typical cases in which hypertension and generalized vascular disease have become the most outstanding features of a long standing *chronic glomerulonephritis* the retinitis is associated with sufficient evidences of arteriosclerosis to resemble closely the retinitis of malignant hypertension. Patients with chronic glomerulonephritis rarely live long enough after the development of retinitis to allow the retinitis to heal completely. If the retinitis does subside however the end picture is that of any retinitis of edematous or vascular origin: pallor with some blurring of the disk, secondary arteriosclerosis and atrophy and degeneration of the retina with proliferation and clumping of pigment especially in the macular region and periphery. The arteriosclerosis which follows retinitis is different from that seen in hypertensive disease without retinitis and is characterized by irregular narrowing of the vessels with loss of transparency of the walls and perivascular thickening and infiltration involving the veins as well as the arterioles.

This typical albuminuric retinitis is seen most commonly in the terminal stages of *chronic glomerulonephritis*. Its evolution can be watched more readily however in cases in which the condition passes from acute nephritis with little if any quiescent period into a subacute phase with progressive renal insufficiency. In acute glomerulonephritis as ordinarily seen retinal changes are not found. Perhaps in most cases mild retinitis develops at the onset and is characterized by mild hyperemia or ischemia of the disk, some arteriolar constriction, mild edema of the retina and a few flame-shaped hemorrhages in the vicinity of the disk (acute angiospastic retinitis). This retinitis however may last only a few days and may leave only slight residuals, thus the majority of patients with acute nephritis will show normal fundi. The fundi remain normal until the terminal stage of the nephritis is heralded from the ocular standpoint by the usually sudden appearance of retinitis. During the quiescent period no changes in the arterioles are visible by means of the ophthalmoscope. The retinitis then develops without preceding arteriosclerosis and is distinguished by this fact from the retinitis of primary hypertensive disease. Constriction of the arterioles is usually apparent at the onset of the retinitis. The primary changes in the retina itself are edema and hemorrhage. Part and at times most of the edema is subretinal. While this retinitis is most often of angiospastic origin edema of the retina is associated in some cases of severe generalized edema and may be

in part at least of the same origin as the general edema. In such cases it shifts as does the general edema, with the position of the patient in bed and can be markedly increased if the head is lowered, and decreased if the head is elevated. This is not true of edema of the fibrinous stage or type usually seen in 'albuminuric' retinitis.

In subacute glomerulonephritis the retinitis is often as severe as it is in chronic glomerulonephritis. In some cases however a

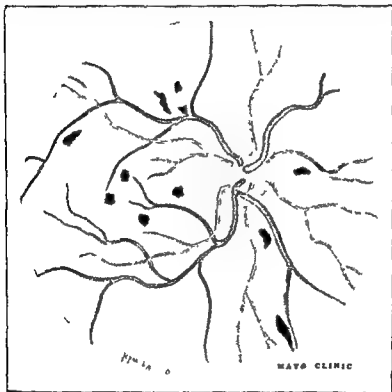


FIG. 133. Retinitis of subacute glomerulonephritis.

much milder form is seen with only slight edema of the retina and a few cotton wool patches and hemorrhages. Such retinitis is indistinguishable from that of severe benign hypertension except by the absence of arteriosclerosis (Fig. 134).

In most cases of chronic glomerulonephritis the retinitis is of the edematous or vascular type just described. In some cases, however from the standpoint of the retina the secondary anemia associated with the renal insufficiency seems to be the dominant

factor. In such cases mild retinitis will be seen hardly distinguishable from that found in pernicious anemia or in anemia secondary to carcinomatosis. The disk is definitely anemic and scattered superficial cotton wool patches and hemorrhages usually of the irregularly round type with white centers characteristic of anemia are found in a slightly edematous retina. The retinal arterioles are likely to be constricted instead of dilated as they are in the other types of anemia. This is the main distinguishing feature.

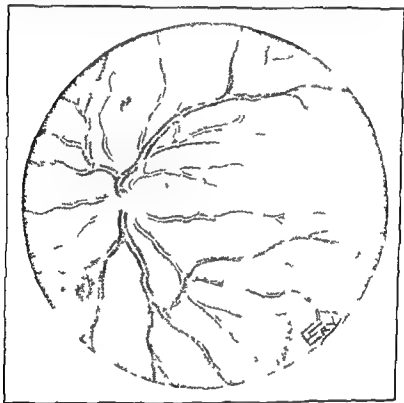


FIG. 135. Retinitis of anemia in nephritis.

and is not constant. It is dependent probably on the elevation of the blood pressure. Retinitis of this type is seen only in cases in which the secondary anemia is severe and in which the concentration of hemoglobin is less than 40 per cent (Dare). It is not clear why this retinitis develops in place of the typical retinitis of nephritis (Fig. 135).

In most cases of primary glomerulonephritis there is not any visible sclerosis of the retinal arterioles prior to the onset of retinitis.

## RETINITIS IN NEPHRITIS

The arterioles become sclerosed in the course of the retinitis but the residual sclerosis seen after the subsidence of the retinitis in the rare cases of recovery is essentially secondary to the retinitis in which there is persistent hypertension with associated following acute nephritis the residual lesion is a disease rather than a

of arteriosclerosis

Retinal arteriosclerosis is never a

only of the diffuse vascular disease which complicates nephritis is not dependent on preceding arteriosclerosis is clinically obvious. The theory is at least alluring that it is the result of vasoconstriction or vasospasm with capillary ischemia or stasis.

A number of observers have demonstrated rather conclusively that spasm does occur in the retinal arterioles. Spasm of individual arterioles as seen in cases of recurrent transitory obscuration of vision is characterized by sudden complete wiping out of the vessel beyond the point of spasm. If such a spasm disappears promptly as it usually does there is no residual injury. If it

persists for several hours or days the retina degenerates and loss of vision is produced.

Spasm of individual arterioles beyond the point of spasm with resultant edema of the retina can be produced experimentally.

Interference in capillary circulation by edematous and hemorrhagic changes spoken of as retinitis toxica of pregnancy affords the best opportunity for studying the effect of persistent non-obliterating spasm of the retinal arterioles.

In toxemia of pregnancy the retinal changes suggest acute vascular spasm or hypertensive disease rather than glomerulonephritis. In this disease the effects of a sudden or rapidly rising hypertension are best seen. The first visible sign is constriction of the arterioles definitely spastic in type. The constriction does not involve all the vessels uniformly and its intensity varies at different points in the course of the same arteriole. An appearance of irregular constriction is produced which is similar to that seen in arteriosclerosis. It may be interpreted as sclerosis if the patient is seen for the first time in the stage of tonic contraction. But these constrictions are really spasms and if carefully watched in the early stages they will be seen to shift their situation in the vessel and to change in degree of constriction as well as in position. Complete obliteration of the arteriole beyond the point of spasm never occurs. If the toxemia persists these varying spasms become tonic and fixed and if constriction is sufficiently severe edema, hemorrhage and exu-

dition appear in the retina usually in definite association with the visible points of maximal constriction. Such retinitis is similar to that seen in severe but not malignant hypertensive disease; the main difference is that the disk is more anemic or ischemic in appearance and is more likely to be mildly edematous (Fig. 136).

In certain cases the spastic constriction seems to involve the central artery as well as or rather than individual retinal arterioles.

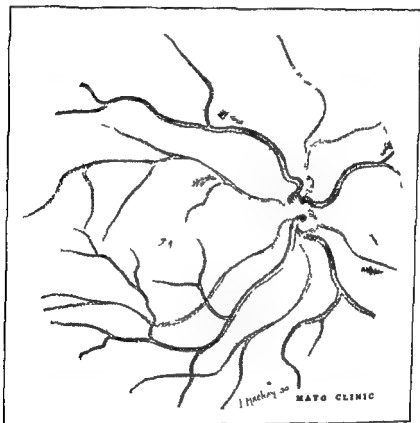


FIG. 136—Retinitis in toxemia of pregnancy

and retinitis results which is like that of glomerulonephritis with edema and anemia of the disk and generalized edema of the retina with superimposed cotton wool patches and hemorrhages. The arteriolar constriction and the retinitis of toxemia of pregnancy usually subside fairly promptly after delivery; the residual injury varying with the severity of the retinitis. If delivery has taken place while the spasms of the arterioles are still varying or clonic in nature, the arterioles rapidly return to normal. If the spastic

constriction of the arterioles has been allowed to persist to the point of inducing edema of the retina the resultant ischemia of the vascular wall or the perivascular edema or both cause permanent injury or sclerosis of a grade dependent on the severity of the constriction or of the retinitis. Evidently similar injury occurs

portionate to the grade of the retinal arteriosclerosis. A patient for example who entered the hospital with toxemia of pregnancy and severe retinitis had residual sclerosis of the retinal arterioles

losclerosis. For the future well being of the patient pregnancy should be interrupted at the first signs of tonic arteriolar spasm with localized edema.

Haselhorst and Milius<sup>1</sup> expressed the belief that the edema of the retina in toxemia of pregnancy results from capillary stasis in the region of maximal arteriolar constriction. They were able to demonstrate stasis in the capillaries of the nail fold coincident with maximal spasm of the retinal arterioles. Convulsions occurred shortly after this stage was reached.

In a few cases of toxemia of pregnancy the circulatory disturbance seems to involve mainly the choroidal vessels. In these cases anemic or ischemic foci appear in the choroid as scattered pale washed-out round patches. These may represent spasms of choroidal arterioles. Following these generalized progressive subretinal edema develops with resultant detachment of the retina which may become total. Lesions in the retina proper may be minimal. A similar sequence of events may be seen at times in subacute glomerulonephritis. Such detachments usually disappear rapidly after delivery with much less residual injury than would be expected from a typical retinitis similarly severe in degree. There is only slight if any residual sclerosis of the arterioles of the retina. In such cases the blood pressure usually returns to normal rapidly. The author has seen one patient who went through two succeeding pregnancies without return of the hypertension or of the toxemia.

## RETINAL LESIONS IN ESSENTIAL HYPERTENSION

Sclerosis of the Arterioles. In many cases of essential hypertension

ently arterioles which measure  $60\mu$  or less in diameter. They share therefore in the general involvement of the arterioles throughout the body. As seen with the ophthalmoscope the first alterations that take place in the arterioles of the retina are narrowing of the caliber, a change to a lighter color than normal of the entire breadth of the arteriole and exaggeration and broadening or accentuation of the reflex stripe. These are regarded by some as signs of hypertension in the sense of spastic arteriolar constriction or increased arteriolar tonus and by others as the commencement of actual arteriosclerosis through thickening of the media. In more advanced cases signs of definite sclerosis appear irregularities of the lumen of the arterioles, compression of the veins at the arterial crossings and at times visibility of the vascular walls. Irregularity of lumen is the most definite sign of sclerosis if it is not confused with the irregularity produced by spasm. Severity of sclerosis can be graded from 1 to 4 largely on the basis of the number of irregularities and the degree to which they narrow the lumen of the arterioles. Sclerosis observed in advanced cases is visible in all branches but in earlier stages is best seen in the smaller arterioles either in the nasal or in the secondary and tertiary branches of the temporal vessels. It is usually rather evenly distributed in grade in all vessels of approximately the same size. As has been mentioned a certain amount of visible thickening of the vascular wall may occur in some cases but in the main definite perivascular infiltration is seen only when retinitis with edema of the retina has been present previously. Primary periarterial and perivenous thickening occurs more often in inflammatory disease of the vessels such as that seen although rarely in vascular syphilis or tuberculosis.

In the senile retina the arterioles are attenuated but do not have the burnished color which indicates constriction or thickening of the media. When hypertension is present in cases of this senile type of retina there is also a certain degree of irregularity of lumen in the attenuated arterioles. The veins are usually narrowed as well and there is no arteriovenous compression. This senile sclerosis is rarely more than Grade 1 or 2 in severity. It is more common than the ordinary variety seen in hypertension in persons who are more than sixty years of age and who have mild essential hypertension and coronary sclerosis.

When sclerosis of the hypertension type has developed it remains obvious in the retina even though the blood pressure falls. Its presence therefore even in mild degree is of diagnostic value in cases of cardiac decompensation since it indicates even if the blood pressure is normal or low that the cardiac disease is entirely or in part on a basis of hypertension. This has been proved by

the clinical studies of O'Hare and Walker<sup>4</sup> and by the clinical and postmortem studies of Yater and Wagener.<sup>5</sup>

In mild practically non progressive hypertension there is little if any visible increase from year to year in the sclerosis of the retinal arterioles. It will be found to be graded the same on repeated visits. If the sclerosis is found to increase definitely in grade as the patient is kept under observation it can be assumed that the hypertensive disease is progressive. From time to time small hemorrhages may be seen in the retinas of such patients. They do not mean necessarily that the disease is not relatively benign and they are not indicative of renal insufficiency. They have no more serious significance than the degree of arteriosclerosis with which they are associated but they do indicate that the hypertension is of progressive type.

**Retinitis.** Exclusive of sclerosis the lesions which occur in the retina in cases of hypertension and which are described under the name of retinitis are those which have been fully distinguished from those due to another feature of the systemic disease which formerly was presumed to be renal insufficiency but which is more probably angiospasm. To the group dependent on arteriosclerosis belong thrombosis of the retinal veins and the retinitis of arteriosclerosis. To the angiospastic group belong the retinitis of severe benign or intermediate hypertension the retinitis of malignant or fulminating hypertension and acute angiospastic retinitis.

Even in benign non progressive hypertension sclerosis of the retinal arterioles not necessarily of high grade may be complicated by venous thrombosis. Thrombosis of the central vein of the retina or of one of its branches is usually unilateral and in the latter case the edema, hemorrhage and exudation are confined to the area of the retina drained by the thrombosed vein. Recent thrombosis of the central vein is characterized by the presence of a pale cyanosis of the veins at the periphery of the retina as a rule only in the later stages. In thrombosis of a branch vein the obstruction to the circulation occurs most often at an arterial crossing and careful search usually will reveal the portion of the vein central to the point of obstruction to be empty and the dilated and cyanotic distal portion to be hidden under more or less massive hemorrhages (Fig. 137). The diagnosis is even more readily made in the later stages when the edema has subsided and the hemorrhages are being absorbed. Healing takes place either by canalization of the obstruction or through the establishment of anastomotic circulation by the formation of tortuous new channels or the dilata-



tion of previously existing small channels of communication with other veins. Hemorrhages will recur over a long period unless the anastomotic circulation is competent. The degree of healing may furnish an index of the flexibility of the general vascular system.

In a certain number of these cases of venous thrombosis the end result is a picture not unlike that of the retinitis of arteriosclerosis.



FIG. 137.—Recent thrombosis of the inferior retinal vein.

described by Moore.<sup>2</sup>

crete hard looking patches in the vicinity of small term

may be found in any portion of the retina but they are usually confined to one area and not generalized throughout the retina. Typically they are associated with rather severe arteriosclerosis and are the result of the local obliterative vascular lesion. From the standpoint of general diagnosis and prognosis therefore they are

no more significant than the arteriolosclerosis itself. The *retinitis of arteriosclerosis* is often unilateral. It is relatively rare and indicates a tendency to cerebral hemorrhage rather than to terminal renal insufficiency. Because of its different mode of origin and its different prognostic significance it should be distinguished from those varieties of retinitis which are dependent on the vasoconstrictive rather than on the sclerotic element of the hypertensive disease (Fig. 13S).



FIG. 13S. Retinitis of arteriosclerosis.

The *retinitis* which is most characteristic of hypertensive disease is basically angiospastic and not angiosclerotic. It is associated with arteriolosclerosis but its severity is by no means proportionate to the grade of the sclerosis. The grade of the sclerosis may serve as

such retinitis always means that the hypertension is of progressive type. But it is possible to divide cases of hypertensive disease and angiospastic retinitis into two groups, severe benign or inter

The retinitis of severe benign or intermediate hypertension is characterized by hyperemia of the disks, moderate constriction of the arterioles that is greater in spots, varying grades of arteriosclerosis and scattered cotton wool patches and hemorrhages in the retina. Mild generalized or localized edema of the retina may be present in the early stages and may leave in the later stages scanty feathery white punctate residues. This type of retinitis tends to clear up rapidly under proper treatment of the hypertension and the hypertension usually can be well controlled for a number of years. The retinitis tends to recur, however, as the hypertension



F 139 — Retina of severe benign hypertension

progresses. In the recurrences edema of the retina is likely to be more definite. The narrowing of the margins of the macula is never

The hypertensive disease in cases of retinitis with measurable edema of the optic disks is almost invariably of a rapidly progressive and fatally

malignant pathognomonic of the retinitis proper which is diagnostic. The sclerosis is often less marked than in the retinitis of arteriosclerosis or in that of

severe benign hypertension, and there is often comparatively little

hemorrhages are also present in the later stages, the smaller, feathery white spots characteristic of receding edema appear, especially in the macular regions with the formation of partial or complete macular stars. In this stage the early constriction of the arterioles may be replaced by secondary relaxation and clumping of pigment

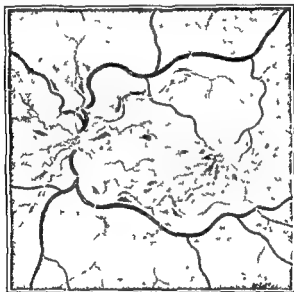


FIG. 140.—Retinitis of malignant hypertension

in the choroid and the retina may be seen as the edema recedes from the periphery. In some cases however the lesions in the retina are so minimal that it is necessary to depend on the condition of the arterioles to distinguish the edema of the disk from the choked disk of cerebral tumor. The edema of the disk in these cases of malignant hypertension may be due in part at least to increased intracranial pressure since the pressure of the spinal fluid is found to be increased in the majority of the cases and the edema has been found to recede in some after spinal drainage (Fig. 140).

As a rule the retinitis of malignant hypertension persists for the duration of the patient's life. In a few instances however, it

subsides although the patient continues his downhill course. In such cases the edema of the disk is the most persistent feature. The end picture is a full pale disk with blurred margins, a high grade of sclerosis of the retinal and choroidal arterioles usually with secondary perivascular deposits and atrophy of the retina and choroid with clumping of pigment especially in the macular region and periphery. The picture is not unlike that seen after severe retinitis accompanying toxemia of pregnancy.

The general prognosis is as serious in the case of healed retinitis as in persistent retinitis. Few of these patients will live more than eighteen months to two years after the retinitis has been observed and the majority die in a much shorter time. The retinitis is not confined to any age group. It occurs in children aged less than ten years and in persons aged more than sixty years but it is seen most often between the ages of forty and fifty-five years. Most of the patients will have terminal renal insufficiency. The retinitis is often seen however and the patient may die while renal function is still good. The retinitis obviously is not dependent therefore on renal insufficiency. The striking constriction of the arterioles in all the early cases often in the presence of minimal sclerosis especially in children seems to justify the interpretation of this

ension is of the albuminuric  
ts to the retinitis of chronic

glomerulonephritis. The edema of the retina is less likely to be of the dense white coagulating type and detachment of the retina is less common. Individual cotton wool patches are a more outstanding feature. Most important however is the presence of arteriolosclerosis of the hypertension type which is absent in the early stages of the retinitis of glomerulonephritis. In cases in which the edema of the retina is not sufficient to mask the arterioles differential diagnosis on this basis is comparatively easy. If the arterioles are concealed by edema or if they are the site of perivascular thickening and sclerosis secondary to edema it is often difficult to be sure of the presence or absence of preexisting hypertension sclerosis and hence to distinguish definitely between the retinitis of malignant hypertension and that of chronic glomerulonephritis. Careful study of the smaller arterioles in the less edematous periphery of the retina may make possible a correct diagnosis. The color of the disks often is helpful in the differentiation of these cases. The disk in chronic glomerulonephritis usually is pale because of the secondary anemia associated with the renal insufficiency. The disk in malignant hypertension always is hyperemic except in the fourth or healed stage of the retinitis when secondary atrophy of the nerve has occurred.

**Acute Angiospastic Retinitis**—In some cases of rapidly rising blood pressure in *acute nephritis* or in *diffuse vascular disease*, a retinitis occurs which is characteristically angiospastic but which in its early stages shows no organic lesions in the arterioles and no definite choking of the disks. In acute nephritis and in a few cases of diffuse vascular disease this retinitis may subside with little or no residual arteriosclerosis. In most cases of diffuse vascular disease however arteriosclerosis soon develops and its character, together with the course of the retinitis will often indicate the severity and prognosis of the general vascular disease. In the acute phase of the retinitis an active lesion of the intima of the arterioles may be evidenced by the occurrence of thrombosis in one or more small arterioles. Such cases usually progress rapidly to a fatal termination. In a few however the retinitis subsides leaving only a residual arteriosclerosis with obliterated small arterioles.

tion in the  
the retinitis  
of the arterioles and choking of the disks develop. In these cases the hypertensive disease runs the characteristic malignant or fulminating course.

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## CHAPTER XXXVIII

### THE PATHOLOGY OF THE OCULAR CHANGES IN NEPHRITIS AND HYPERTENSION

By JONAS S. FRIEDENWALD, A.M., M.D.

**Introduction The Pathogenesis of Albuminuric Retinitis**—The history of thought in regard to the pathogenesis of albuminuric retinitis exhibits marked fluctuations pendulum swings characteristic of the slow advance of knowledge. That visual symptoms occurred in the course of chronic nephritis was recorded by Bright<sup>1</sup> in his classical treatise. The fathers of modern ophthalmology von Graefe and his pupils described the ophthalmoscopic appearance of albuminuric retinitis and named it. We now recognize that it is not an inflammatory condition that the term retinitis is a misnomer and that albuminuria is only indirectly connected with the retinal lesion. Still the old name remains in common usage and answers the purpose of attaching a label to a clinical entity.

The first important anatomical investigations in this field were

to whom we are indebted for the first comprehensive study of the relation of retinal arteriosclerosis to general vascular disease led to the general acceptance of the notion that albuminuric retinitis is chiefly a vascular affection. In 1907 Schieck<sup>2</sup> demonstrated sections from 2 cases of marked albuminuric retinitis in which he had been unable to find any serious vascular lesions. This led to investigation of other possible causes of the retinal affection. In 1903 Vidal<sup>3</sup> and Rochon Duvigneaud and Opin<sup>4</sup> advanced the theory that the retinitis was a toxic affection produced by non-protein nitrogenous substances retained in the blood. This theory met with wide approval and was accepted by Leber<sup>5</sup> in 1909 but growing clinical knowledge soon revealed that nitrogen retention occurs in uremia due to urinary obstruction just as much as in chronic nephritis but retinitis does not occur in uremia of urinary obstruction. Direct toxic action upon the retinal nerve elements from retained nitrogenous waste products or from some unknown toxin of hypertension or arteriolosclerosis has never been demonstrated. The modern theory of the vascular basis of albuminuric retinitis seems an adequate explanation without the aid of hypothet

ical toxins. This does not exclude the possibility of a toxic effect. The question remains open.

Cohen<sup>8</sup> in 1922, drew attention to changes in the blood vessels in the choroid in albuminuric retinitis and somewhat cautiously, suggested that the cause of the retinal affection might lie there. An extensive study by Wood<sup>10</sup> on choroidal arteriosclerosis had already shown that changes in these vessels are extremely common in late middle life even in the absence of general arteriosclerosis. The changes found by Cohen in albuminuric retinitis do not appear to exceed those found in the choroid in otherwise normal persons. The author's experience fully confirms the findings of Wood. In respect to vascular changes the choroid resembles the spleen showing marked sclerotic change in almost every individual over fifty years of age quite irrespective of the presence of general arterial disease.

Another suggestion is that of Hanssen and Knack<sup>11</sup> who in 1917

arterial inflammatory nodules in the choroid in some instances with in others without albuminuric retinitis. They concluded that the retinitis is an inflammatory lesion. In the seventeen years since the publication of Hanssen and Knack's paper 4 cases have been reported showing inflammatory lesions similar to those described by these writers. Three of these were cases of generalized periarteritis nodosa—2<sup>12, 13</sup> without and 1<sup>14</sup> with albuminuric retinitis. One additional case of chronic nephritis albuminuric retinitis and terminal *Streptococcus viridans* septicemia showed the same lesion.<sup>14</sup> One is forced to conclude that Hanssen and Knack were misled by the concurrent presence of some infectious disease. Many of their cases were instances of trench nephritis while others suffered from relapsing fever.

Volhard<sup>15</sup> has attributed the retinal lesion to vascular spasm with resultant retinal ischemia. This theory is not subject to direct proof but is indirectly supported by the report of Schieck and others who were unable to discover morphological evidence of vascular disease in some cases of albuminuric retinitis.

New light was thrown on the subject by Verwey<sup>16</sup> who used frozen sections and fat stains in the study of his cases. He found in all cases of albuminuric retinitis evidence of arteriolar sclerosis in the retina. The characteristic picture is that of a hyaline thickening of the arterial wall the hyaline containing large amounts of some as yet unidentified lipid which stains deeply with Scharlach R and allied dyes. He examined a considerable number of cases of general and cerebral arteriosclerosis and found that in no instance was there arteriolar sclerosis of the retina.



The incidence of retinal arteriolar sclerosis in vascular and renal disease is of interest. As stated above it does not occur in senile arteriosclerosis in which atheromatous lesions are most prominent. It occurs almost invariably in general arteriolar sclerosis no matter whether the kidneys show marked lesions or not. With equal frequency it occurs in arteriosclerotic nephritis in some instances of which the kidneys and retinae alone of all organs show marked arteriolar lesions. Finally it occurs in many cases of chronic arteriosclerotic nephritis and of chronic glomerulonephritis even when there are no arteriolar lesions in the kidneys or in any other organ. We are forced to conclude that the retinal arterioles are especially susceptible to damage by that agent as yet unknown which is the cause of arteriolar sclerosis.

All forms of progressive renal degeneration may be complicated by retinitis or fail to show such lesion. However a comparison of the kidneys of retinitis cases with those of progressive renal disease without retinitis reveals on the average more polymorphonuclear infiltration and other evidence of active kidney destruction in those cases with retinitis than in those without it. It is difficult to estimate such matters quantitatively but the study of a considerable series of such kidneys has led the author to believe that the rate of destruction of the kidney parenchyma and the concentration of Volhard's vasopressor (vasotovin?) is intimately connected with the development of the retinitis. This is in accord with the clinical fact that renal function goes rapidly down hill when or soon after the retinitis develops.

**Retinal Changes** — In view of the importance of retinal arteriolar disease in the pathogenesis of albuminuric retinitis it is necessary to digress for the moment to discuss the nature of retinal vascular disease in general and especially the morphology of the structural changes recognizable with the ophthalmoscope upon which clinical diagnosis is based. These ophthalmoscopically visible changes are the following:

- 1 Beading of the vessels localized variations in caliber
- 2 General constriction or dilatation of the arteries
- 3 Arteriovenous constriction
- 4 Increased visibility of the vessel walls
- 5 Copper wire and silver wire vessels
- 6 Changes in the light reflex over the vessel

### ANATOMY OF THE RETINAL VESSELS

Before entering upon the morphological basis for these ophthalm-

circumstances the retinal vessels are called upon to sustain an internal pressure approximately equal to that sustained by vessels of equal size in other organs. The pressure in the terminal arterioles is perhaps somewhat higher than the average because the capillary pressure in the eye is higher than in any other organ barring the effects of gravity. The gradient of pressure fall from the central retinal artery to the capillaries must, therefore be somewhat less than in other organs.\* The intraocular vessels however are aided in supporting their internal pressure by an external pressure of some 20 mm Hg namely the intraocular pressure. On account of the high capillary and venous pressure within the eye the relief of the intraocular pressure gives to the vascular tree is manifested mainly in regard to the larger arterial branches. It is perhaps as a response to this relief from internal strain that the unusual delicacy of the retinal arterial wall is to be understood. This delicacy of structure may explain the unusually great local effects of changes in blood pressure if these local effects are truly disproportionate to those in other organs and not merely more easily recognizable. The retinal artery in its course through the orbit and optic nerve has a thick muscular coat similar to that of other vessels of similar size but on passing through the cribriform plate into the eye the arterial coat abruptly dwindles to about one third its previous thickness. The intima remains unchanged the elastic lamella is at first preserved somewhat reduced in density but disappears from the secondary or tertiary arterial branches in the retina the adventitia becomes thinner and looser in structure. The greatest change in the vessel on entering the eye is in the media which becomes reduced to a thin layer usually less than one-tenth the diameter of the vessel in thickness. It is difficult to demonstrate histologically the presence of smooth muscle fibers in the media of the retinal arterial branches. That contractile elements are present is undoubted on clinical and experimental grounds. On account of the thinness of the retinal arterial walls and their considerable variation under normal conditions and also on account of the difficulty of estimating the functional internal diameter of collapsed retinal vessels seen in microscopic sections minor changes in thickness of the arterial walls are difficult to recognize on microscopic examination. In the larger arterial branches in the retina the intima is sufficiently developed to allow atheromatous degeneration similar to the changes in larger arteries in arteriosclerosis. These vessels may also show hyaline degeneration of the media characteristic of arteriolosclerosis. It is of no interest whether these vessels are arteries or arterioles. The important fact is that they are capable of partaking differently, in two different disease processes of

\* For a thorough discussion of the intraocular vascular pressure the reader is referred to an article by Duke-Elder.

the vascular tree and that therefore the careful clinical study of these different forms of vascular degeneration in the retina is of importance diagnostically and prognostically.

A further peculiarity of the retinal vascular tree is the crossing of the retinal arteries and veins. The retinal vessels excepting only the finest twigs and capillaries are spread out in a two-dimensional plane with the result that the arteries and veins are brought into intimate contact with one another at points of crossing. In other organs the large arteries and veins often lie in a common sheath like the central retinal vessels in the optic nerve, while the smaller twigs of the arteries and veins branch apart and have no connection with one another except through the capillaries. An exception to this rule outside of the retina is found in the afferent and efferent vessels of the kidney glomerulus. Whether this fact is significant in the physiology and pathology of the kidney the author leaves to other participants in this volume.



FIG. 141. Arteriovenous crossing in the retina. Vein above the artery.

The histology of the retinal arteriovenous crossings has been studied carefully by Koyanagi.<sup>20</sup> At the points of crossing the vessels have a common adventitia which surrounds them without extending into their wall of contact. Here the media of the artery is in direct contact with the inner layers of connective tissue of the venous wall so that it becomes impossible to say where one begins and the other ends. The total thickness of this common wall is not significantly greater than the arterial wall alone at other points. The consequences of this intimate binding together of arteries and veins will be discussed in regard to the so-called arteriovenous constriction and in regard to venous sclerosis.

#### CHANGES OPHTHALMOSCOPICALLY VISIBLE IN RETINAL VASCULAR DISEASES IN GENERAL

**Localized Variations in Arterial Caliber**—The phenomenon of beading of the retinal arteries was first described by Raehlmann.<sup>27</sup>

who also studied its histological significance. He described the condition as produced by a localized proliferation of the intima resulting in small mound like protrusions into the vessel lumen.



FIG 14<sup>b</sup> Atheromatous plaques in a retinal artery drawn from a case of albuminuria retinalis in which the retina was at necrosis (Sudan III and examined without sectioning).

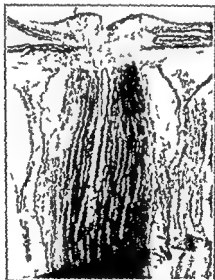


FIG 143—Atheroma of the central retinal artery in a case of albuminuria retinalis (section stained with Sudan III)

His observations were confirmed by (cat) and a number of other investigators. A study of the illustrations of these workers will convince anyone familiar with modern histological technique that they were describing small atheromatous plaques. Such atheromata

occur commonly in the larger branches of the retinal arteries but are not found beyond the tertiary branches. Beading of the smallest vessels is due to a different process, an irregularly distributed hyaline degeneration of the vessel wall.

Histological studies show that atheromata occur more frequently in the central retinal artery in its intraneural course than in the retinal branches. Favorite sites are at the points where the vessel enters the optic nerve sheath and where it passes through the cribriform plate. The presence of scattered minute atheromatous plaques in the retinal branches may be considered as the visible outposts of a process which is more developed in the central arterial stem beyond the view of the ophthalmoscope.

A few writers have maintained that beading of the arteries may be due to local spasm, but the usual persistence and immobility of the lesion are against this interpretation in most cases. On the other hand, transient localized constrictions of the arteries are not uncommon in the toxemias of pregnancy and in arteriolar sclerosis as noted above. This phenomenon however is to be differentiated from the more frequent stationary beading of the vessels.

**General Changes of Arterial Caliber**—In a variety of conditions the retinal arteries are diffusely dilated. The cause may be local such as eye-strain or local inflammatory diseases or general such as congenital heart disease, leukemia, polycythemia, fever, etc. Such states are functional without histological equivalents. In

older cases the larger retinal branches may be diffusely dilated. In these cases the condition is purely functional and not associated with any morphological changes in the arterial wall. The author has not seen in a retinal artery a simple hypertrophy of the media which might be considered as a functional response to long-continued hypertension.

A very common finding in the early stages of albuminuric retinitis consists in areas of capillary hyperemia scattered throughout the retina, often surrounding the cotton wool spots. In these regions the capillaries not only are dilated but also present tortuous varicosities. In some instances the varicosities may be seen in post mortem specimens. If the foregoing theory of the relation of vascular spasm to arteriolar sclerosis is correct, these areas of capillary hyperemia may represent the physiological response to anoxemia of the adjacent tissues.

Diffuse constriction of the whole retinal arterial tree is commonly seen in the atrophic stages of local disease and in cases of arteriosclerosis with hypertension. The clinical correlations and signifi-

cance of this and other ophthalmoscopic findings in arteriosclerosis and hypertension have been discussed at length in an article by H. Friedenwald and the author,<sup>10</sup> and will not be dealt with here

lumen by a thickening of the arterial wall. In these cases, very marked atheromatous changes in the neural portion of the central retinal vessel are found. The retinal vessels presumably are narrow because the central stem behind the disk is partially obstructed and the pressure within the retinal branches reduced. It has been argued that the diffuse constriction of the arterial tree in the late stages of albuminuric retinitis is unlike that commonly seen in old people, and that, while the latter may be due to atheromatous changes farther back in the arterial tree, the former is due to spasm. Against this interpretation is the fact that those cases show marked atheroma of the intraneural portion of the vessels and cannot be dilated by amyl nitrite or histamine as the author has repeatedly found.

In many of these cases, especially in old people, the retinal arteries are not only narrow but straight and branch at acute angles, giving the appearance of having been drawn into the disk. It is possible that the sclerotic process in the central stem may be characterized not only by an encroachment on the lumen, but also by a shrinkage in length as Thoma<sup>22</sup> suspected in relation to the vessels of the limbs. General reduction in the caliber of the retinal arteries is the end-stage of the process that first manifests itself in beading of the arteries, and the two conditions are often seen together. As has been noted above, these cases when not complicated by local disease or cardiac decompensation or similar cause of temporary reduction in blood-pressure, invariably have hypertension. It seems likely that these cases belong to the group studied by Gull and Sutton<sup>23</sup> and later by Bordley and Baker,<sup>2</sup> in which a close correlation was established between the blood-pressure level and pathological findings in the arteries of the medulla oblongata, the arteries involved being similar to the central retinal vessels in size.

**Arteriovenous Constriction.**—From the anatomical peculiarities of the arteriovenous crossings, it is obvious that a constriction of the vein at the point of the crossing may be produced in several ways. 1. If the artery is displaced as a result of increased or decreased tortuosity it must drag the vein with it and if the drag is sufficient produce a constriction at the crossing. This perhaps ought to be spoken of as arteriovenous displacement. It occurs in conditions in which the tortuosity of the arteries has recently been increased and in the cases of shrinkage of the arterial tree

mentioned above. It has been credited as a sign of hypertension though in fact it may occur without change in the blood pressure. No histological changes are associated with arteriovenous displacement unless marked venous stasis is produced.

2 If the arterial wall becomes thickened and its external diameter increased it must encroach upon the space within the common arteriovenous adventitia and constrict the lumen of the veins. Such conditions are found in cases of retinal arteriosclerosis when in addition to atheromatous plaques of the intima a fibrous thickening of the media and adventitia is present. This need not be associated with hypertension or renal disease but is due to retinal

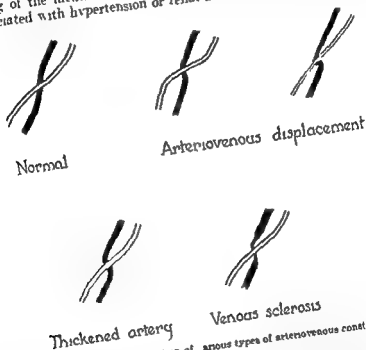


FIG. 144—Schematic illustration of various types of arteriovenous constriction.

arteriosclerosis. More commonly the thickening of the vessel wall is due to arteriosclerotic thickening of the media with hyaline degeneration. This is invariably associated with hypertension and sooner or later complicated by renal disease. The condition can be recognized ophthalmoscopically when the vein is seen to curve sharply around the artery without necessarily being displaced laterally in its course.

3 Owing to the fact that the arteriovenous wall is a single indivisible structure sclerotic changes in the artery may extend into the vein sometimes reaching up and down the vein for a short distance from the crossing. This accounts for the extraordinary

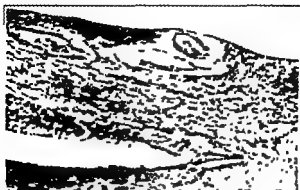


FIG. 145 — Arteriovenous crossing in a case of generalized arteriosclerosis. Note thickened adventitia.

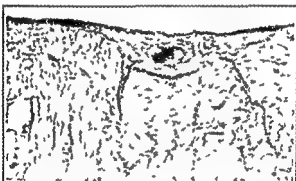


FIG. 146 — Arteriovenous crossing in a case of albuminuric retinitis. Note thickened adventitia and atheromatous plaques in both vessels.

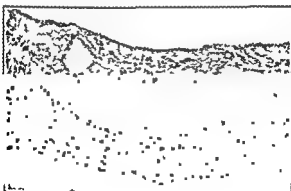


FIG. 147 — Fat granule cells about the veins in the regressive stage of a case of albuminuric retinitis. These veins showed intense perivascular stripes on ophthalmoscopic examination shortly before death.



frequency of retinal venous sclerosis and thrombosis. Veins of this size in other organs show such lesions only with the greatest rarity. Ophthalmoscopically this sclerosis of the retinal veins can be recognized by a narrowing of the venous blood column for a short distance on either side of the crossing. This phenomenon is the result of arteriosclerosis not of hypertension and may occur in the absence of hypertension or renal disease. This explanation of the cause of venous sclerosis is important because of the light it sheds on the problem why the small veins in the retina so commonly suffer from sclerosis and thrombosis while veins of similar size in other organs are hardly ever affected by these lesions.

**Increased Visibility of the Vessel Walls**—The normal invisibility of the vessel walls is the result of the fact that they are optically homogeneous structures. Optical inhomogeneity is produced by fibrosis of the media or adventitia. This can be seen in the larger vessels in cases of postneuritic optic atrophy in which there is connective tissue and glial proliferation in the vessel sheath. A similar condition occurs occasionally in the advanced stages of retinal arteriosclerosis. In the smallest arterioles the hyaline degeneration of arteriolosclerosis is associated with large amounts of lipoid. When this process becomes advanced in a small vessel the wall becomes visible as a silver wire. In the larger vessels the hyaline degeneration is associated with much lipoid and the blood column is increased but in uric retinitis and damage need not be due to sclerotic changes but is often the result of an infiltration of the perivascular spaces with large mononuclear wandering cells engaged in removing lipoid and other cellular debris from the injured retina.

that the appearance of copper wire and silver wire arteries represented advanced grades of retinal arteriolar sclerosis with hyaline thickening of the media. In several cases which the author was able to examine microscopically shortly after fundus drawings had been made he was able to confirm Foster Moore's findings. This change is of importance since it represents the advanced stage of the particular vascular lesion which precedes and accompanies albuminuric retinitis.

**Changes in the Vascular Light Reflex**—The light streak on the retinal vessels has been elaborately discussed by Dimmer,<sup>2</sup> Kreiker and H. Friedenwald,<sup>3</sup> each of whom reached somewhat different conclusions as to the physical basis of this reflection. The more

recent studies of Wilmer and his co-workers<sup>29</sup> have confirmed and extended the conclusions of H. Friedenwald as follows. Reflection of light can occur in transparent media only at surfaces separating media of the different refractive indices. Over the

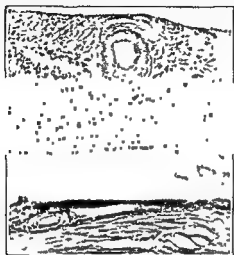


FIG. 14I.—Hyaline degeneration and thickening of the media of a large retinal artery in a case of albuminuric retinitis. This vessel had the appearance of copper wire on ophthalmoscopic examination shortly before death.



FIG. 14J.—Hyaline degeneration of the small arterioles in the retina in a case of albuminuric retinitis. The minute vessel on the left has a lumen smaller than the diameter of a red blood cell.

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retinal arteries reflection can take place at the retinal surface at the boundary between adventitia and media and at the endothelial surface. The reflection by the retinal surface is very brilliant and can usually be separated from that of the arterial wall by slightly tilting the ophthalmoscope mirror. The adventitia has normally the same index of refraction as the surrounding retina and does not contribute to the reflex. Increased width of the arterial reflex relative to the width of the blood column occurs when there is thickening of the media. Increased brightness of the reflex occurs when, as in hyaline degeneration of the media, the index of refraction of the media is increased. This is responsible for the copper wire appearance of the larger retinal vessels in retinal arteriolar sclerosis.



FIG. 100. Extensive hyaline degeneration of a retinal arteriole with complete occlusion of the lumen. This vessel had the appearance of a silver wire on ophthalmoscopic examination shortly before death.

### **PATHOLOGICAL CHANGES IN RETINAL VASCULAR SCLEROSIS**

**Summary** — A consideration of the changes in the retinal blood vessels in vascular disease leads to conclusions and suggestions which may be of importance in the interpretation of vascular disease in general. Naturally such conclusions based on the study of a single organ are tentative. However a volume of this kind seems the appropriate place to state such tentative hypotheses which fit well the data of a single small field leaving to other contributors the decision as to whether these data fit equally well other fields in the general domain.





- (b) Fat droplet cells
- (c) Scarring of the retina and glial proliferation
- (d) Cystic degeneration

All these morphological changes may occur isolated or combined in other retinal diseases. The characteristic feature of albuminuric retinitis is the combination of these changes and their anatomical distribution resulting in the production of a recognizably specific ophthalmoscopic picture.

**Retinal Edema**—The characteristic feature of the retinal edema

cerebrospinal fluid pressure and the edema of the optic disk may be explained as the superposition of the ordinary process of choked disk due to increased intracranial pressure upon the general picture of albuminuric retinitis.

The cause of the retinal edema cannot be the decreased osmotic pressure of the plasma proteins as in the generalized edema of the nephrotic where retinal edema does not occur nor could any constitutional cause well explain such a localized lesion as the retinal edema of albuminuric retinitis. The same objection can be made against explaining the edema on the basis of changes in capillary blood pressure and capillary permeability.

In searching for some local peculiarity of the macular portion of the retina to explain its susceptibility to edema in this condition one finds that the minute venules which radiate spokewise from the fovea are almost always crossed by the superior or inferior macular arteries before they reach the superior or inferior temporal veins to which they are tributaries. Similar crossings of minute venules by larger retinal arteries are rarely found elsewhere in the fundus and when occurring outside the macula it is in isolated uncommon places so that the affected retina is isolated by the normal

istic location of the retinal edema.

The albuminous fluid which escapes into the retina in part seeps into the vitreous where it cannot be recognized clinically but where it is regularly found in histological sections. In severe cases some fluid escapes from the outer surface of the retina producing a flat detachment. In most cases these detachments remain localized but may in some instances become complete especially in retinitis gravidarum.

Within the retina the extravasated fluid tends to accumulate in certain locations for the understanding of which the detailed anatomy of the retina is needed. Outside of the fovea the retinal capillary bed is divided into two systems.<sup>24</sup> One bed of capillaries lies in the nerve fiber layer the other mainly in the inner molecular layer. These capillary systems are separated by the layer of ganglion cells in which the supporting structure of the retina is especially developed. Extravasations of fluid hemorrhages for instance in one of these layers usually do not cross the barrier in the region of the ganglion cells. In the nerve fiber layer these extravasations tend to spread mainly along the nerve fibers. Thus the flame-shaped hemorrhages occur. If the extravasated fluid is rich in proteins especially fibrin we have a fuzzy grayish mass recognizable ophthalmoscopically as a cotton wool spot.

In the deeper layers of the retina there are two favorite positions for the accumulation of fluid. These are the inner molecular layer (the layer of bipolar cells) and the outer granular layer (the layer of fibrils connecting the nuclei of the rods and cones with the bipolar cells). In both these layers the supporting structure of the retina is feeble and the tissues are readily spread apart resulting in the formation of cyst like spaces filled with fluid. Near the optic disk these spaces tend to run together forming an irregular network pattern. In these spaces the fluid is usually albuminous in character and because it differs little in refractive index from the surrounding retina it is rarely visible with the ophthalmoscope. Occasionally however the network pattern of these extravasations may be seen.

The outer granular layer the second favorite site for the accumu-

debris or when after long standing their protein content becomes very low they appear as white dots and for a long time with a fluid of low protein content but in a progressive disease the protein content increases and they may eventually appear as hyaline or colloid masses. Not all these deposits originate from local edema. Some represent the remains of old petechial hemorrhages or of exudates of plasma.

minuric retin  
turbance ar  
hemorrhage

the underlying lesion and in albuminuric retinitis the star shaped figure at the macula is most frequently produced

**Retinal Hemorrhages**—The retinal hemorrhages require little further comment. Patechial hemorrhages occur in other organs as well as in the eye. The exact mechanism of their occurrence is not known. They are more frequent and numerous where there is venous stasis than elsewhere.

**Cytoid Bodies**—A frequent finding in albuminuric retinitis is a localized thickening of the nerve fiber layer of the retina usually about 0.1 mm. in diameter and one third to one half this in thickness. In the center of these thickened areas one finds curious cell like masses called *cytoid bodies*. They are globular structures some 20 to 30  $\mu$  in diameter with a sharply outlined dense eosinophilic nucleus in the center. They were at first considered pathognomonic of albuminuric retinitis but now are known to occur in all other retinal diseases in which hemorrhages are frequent. They were thought to be swollen varicose nerve fibers in cross-section but studies in serial section show that they are globular not tubular structures.

Arranging a large number of these lesions in such a way as to show their stages of growth and resolution the author reached the conclusion that they represent merely one form of the organization of retinal hemorrhages and ischemic infarcts and that the cytoid bodies are large mononuclear wandering cells which accumulate in reaction to hemorrhage and are partially necrotic. Verhoeff<sup>23</sup> has disputed this interpretation pointing out that similar bodies are found in the gloma of the optic nerve. He believes that the cytoid bodies are of glial origin. The question remains open.

**Detachment of the Retina**—The relation of retinal detachment to the retinal edema has already been commented on. Since the detachment is commonly of small extent it is readily masked by the retinal edema and rarely recognized with the ophthalmoscope. On section it is rarely found absent.

**Arteriolar Occlusion and Retinal Infarction**—A not uncommon occurrence in the course of albuminuric retinitis is the occlusion of one or more small arterioles with resultant infarction of a portion of the retina. Only the two inner layers of cells die as the result of such an injury as the outer layer gets its nutrition from the choroid. Usually there is some hemorrhage at the margin of the infarct. The subsequent course is as usual the debris being removed by phagocytes and the defect being healed by glial and connective tissue proliferation. Occlusion of the terminal arterioles in the retina is a common feature of severe albuminuric retinitis and is responsible for many cotton wool spots. Here the tissue necrosis is not very extensive and healing may take place with little loss of function. During the process of healing the cytoid bodies form



an important part of the histological picture. Vessels of this order cannot ordinarily be seen with the ophthalmoscope, but a good example of the relation of the arterial occlusion to the area of edema and necrosis is shown in Fig. 151.



FIG. 152.—Section of a cotton wool spot similar to that shown in Fig. 151. Edema and necrosis of the tissue with surrounding hemorrhage.

More rarely one sees with the ophthalmoscope *occlusions* of the smallest visible arterial branches, that is, of vessels just one order larger than the terminal arterioles. All instances of this kind which the author has studied were in cases of malignant hypertension, and in all cases the duration of life following this retinal vascular accident was short—six to eight months.



FIG 153 —Late stage of a cotton wool spot in a case of albuminuric retinitis showing the accumulation of cytoid bodies



FIG 154 —Serous exudations in the retina in albuminuric retinitis

**Secondary and Reparative Phenomena**—The destruction of retinal tissue attributed to stasis, hemorrhage etc., brings in its wake a variety of secondary and reparative phenomena. The lipid content of the retina as of the brain is very high, and any local lesion is followed by the accumulation of lipid debris. This is taken up by large mononuclear phagocytes, which engorge the

an important part of the histological picture. Vessels of this order cannot ordinarily be seen with the ophthalmoscope, but a good example of the relation of the arterial occlusion to the area of edema and necrosis is shown in Fig 151.



FIG 151 — Photomicrograph of a 'cotton wool spot' in a case of beginning albuminuric retinitis. The retina was stained with Sudan III and mounted flat on a slide without sectioning. The dark hazy area in the center is the 'cotton wool spot' diffusely stained as the result of beginning lipid disintegration. The arteriole supplying this area is completely obstructed by a hyaline lipid thickening of its wall.

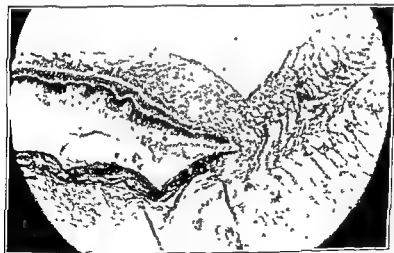


FIG 152 — Section of a 'cotton wool spot' similar to that shown in Fig 151. Edema and necrosis of the tissue with surrounding hemorrhage.

and in all cases the duration of life following this retinal vascular accident was short—six to eight months



FIG 153 —Late stage of a cotton wool spot in a case of albuminuric retinitis showing the accumulation of cytoid bodies



FIG 154 —Serous extravasations in the retina in albuminuric retinitis

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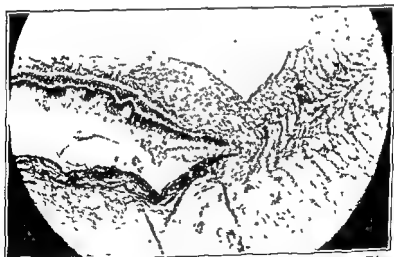


FIG 152.—Section of a 'cotton wool spot' similar to that shown in Fig. 151. Edema and necrosis of the tissue with surrounding hemorrhage.

More rarely one sees with the ophthalmoscope occlusions of the smallest visible arterial branches, that is, of vessels just one order larger than the terminal arterioles. All instances of this kind which the author has studied were in cases of malignant hypertension, and in all cases the duration of life following this retinal vascular accident was short—six to eight months.



FIG 153 — Late stage of a cotton wool spot in a case of albuminuric retinitis, showing the accumulation of cytoplasmic bodies



FIG 154 — Serous extravasations in the retina in albuminuric retinitis

**Secondary and Reparative Phenomena** — The destruction of retinal tissue attributed to stasis, hemorrhage etc., brings in its wake a variety of secondary and reparative phenomena. The lipid content of the retina as of the brain is very high, and any local lesion is followed by the accumulation of lipid debris. This is taken up by large mononuclear phagocytes, which engorge the

fat and distend their protoplasm into a foamy mass filled with fat granules. During the acute stages they are found in large numbers in the retina, tending to accumulate in the same loose layers as the extravasations already referred to. In later stages they migrate away from the lesion by way of the loose tissue spaces about the retinal veins and are ophthalmoscopically visible as yellowish white streaks bordering the veins.

Some of the lipoids liberated by injury, especially cholesterol, are at the margin of the lesion and when present in large numbers are ophthalmoscopically visible either as a line or as a conglomerate mass.

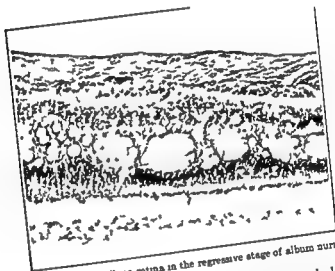


FIG. 155.—Fat granule cells in retina in the regressive stage of albuminuric retinitis.

Eventually the damage is repaired by connective and glial tissue proliferation. In the organization of subretinal hemorrhages the glial proliferation is marked, resulting in the snow bank masses which are sometimes seen in the late stages of albuminuric retinitis but more characteristically in retinitis circinata and other aberrant forms of retinal vascular disease. With the scarring considerable distortion of the retina may occur and the fluid spaces which are found early in the edema may become organized into definite thin-walled cysts lined by proliferated glia. The further course of these atrophic and reparative processes and of the accompanying partial atrophy of the optic nerve is not characteristic.

In the usual case the atrophic and reparative phase is not clearly separated from the stage of active lesions. Fresh hemorrhages and serous extravasations being found side by side with reparative processes. Few individuals suffering with albuminuric retinitis live

long enough to allow completion of the process of repair. In a few cases, collateral venous and arterial channels develop, replacing those obstructed in the course of the disease and the active process

essential difference between the retinal lesions which form the picture of albuminuric retinitis in these three conditions. In all three the retinal vessels show typical arteriosclerotic changes. Cases vary in the speed and malignancy with which the retinal lesions develop. It is natural to expect that those cases in which the vascular disease proceeds most slowly will permit of some circulatory compensation so that the appearance of the ischemic and

On the other hand cases of toxemia of pregnancy and cases of malignant or fulminating nephritis may run their whole course in a few weeks or months. In such instances there is at the outset no ophthalmoscopic evidence of disease of the retinal vessels antecedent to the retinitis. Sclerosis of the terminal arterioles, however, is not wanting. Such clinical distinctions as exist between the retinitis of glomerulonephritis and of pregnancy on the one hand and the retinitis of malignant hypertension on the other seem to be due to the rate of development of the process rather than to any intrinsic differences between them.

**Discussion**—The conception of the pathology and pathogenesis of albuminuric retinitis advanced in these pages may seem unduly morphological. It must then be pointed out that the morphology of the retina is extremely complicated and little known to those

morphology of the retina and its vascular system can the ophthalmoscopic picture be understood and interpreted.

#### OTHER OCULAR LESIONS IN NEPHRITIS AND HYPERTENSION.

Aside from the retinal affections a few other ocular complications of nephritis and hypertension may be briefly mentioned.



**Edema of the Lids**—The loose subcutaneous tissues of the lids like those of the scrotum are specially prone to edema not only in nephritis but also in local inflammatory diseases. Whether this is due to an unusually high permeability of the capillaries or to an unusually low tissue pressure in this region is not known. Early writers were puzzled over the absence of edema of the lids in cardiac decompensation in contrast to its presence in nephritis. Modern studies have removed this difficulty. Nephritic edema is the result of decreased osmotic pressure of the plasma proteins. It exerts an equal force in all tissues and produces the most marked effects in those regions where fluid can most readily accumulate. Cardiac edema is the result of increased venous pressure which enables fluid to leak out of capillaries damaged by stasis. Its most marked effect is in the dependent portions. No cardiac patient could live long with sufficient venous pressure and stasis in his head to cause

a positive von  
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it revealed the

cause of the exophthalmos

**Lipoid Arcus**—The occasional occurrence of a corneal opacity

branches though the stroma of the cornea is also affected the main

mental animals by feeding a diet high in cholesterol it is not unreasonable to assume that the high blood lipid content of nephrosis is responsible for the arcus

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 (Monsieur) F. H. Verhoeff, M.D., F.R.C.S.

# PART VI

## CLINICAL ASPECTS OF BRIGHT'S DISEASE

### CHAPTER XXXIX

#### UREMIA

By FRANZ VOLHARD M.D.

**Introduction** — The most important advance in the understand-

effects of kidney diseases on the whole organism can still be regarded as formerly as results of renal insufficiency, i.e. whether they are renal or not. The question should be asked for each symptom: Does it occur *only* with manifested renal insufficiency or *also* without renal insufficiency?

Hypertension  
as in anuria  
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connected in some way with renal circulation

Renal insufficiency has led to a revision of the old concept of uremia.

Under the term *extrarenal* or *false uremia* we classify a variety of symptoms originating chiefly from the central nervous system that occur even when renal insufficiency is not present. Here we are

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circulatory phenomena occur in chronic primary or secondary hypertension.

#### ECLAMPTIC UREMIA

The clinical picture of eclamptic uremia is characterized by signs of increased intracranial pressure, both general and localized. There are present headache, vomiting, slowing of the pulse-rate, possibly

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# PART VI

## CLINICAL ASPECTS OF BRIGHT'S DISEASE

### CHAPTER XXXIX

#### UREMIA

By FRANZ VOLHARD M D

**Introduction** — The most important advance in the understanding of the problem of kidney diseases is derived from a better insight into the nature of renal insufficiency. This insight has led to the important question whether the well known and severe remote effects of kidney diseases on the whole organism can still be regarded as formerly as results of renal insufficiency, i. e. whether they are renal or not. The question should be asked for each symptom: Does it occur *only with* manifested renal insufficiency or *also without* renal insufficiency?

Hypertension may be observed as a result of renal insufficiency as in anuria. But in the majority of instances hypertension has nothing to do with renal insufficiency though it is a phenomenon connected in some way with renal circulation.

The situation in regard to uremia is more intricate. The question as to which phenomena of this variegated symptom complex occur only with renal insufficiency and which may occur also without renal insufficiency has led to a revision of the old concept of uremia on the basis of a different pathogenesis.

We characterize the phenomena which occur exclusively with renal insufficiency as *true uremia*.

Under the term *extrarenal or false uremia* we classify a variety of symptoms originating chiefly from the central nervous system that occur even when renal insufficiency is not present. Here we are forced to recognize two separate groups. The first acute eclamptic uremia is frequently encountered in acute and subchronic diffuse nephritis and still more frequently in eclampsia of pregnancy but rarely in nephrosis. The second, consisting of the pseudoureemic circulatory phenomena, occur in chronic primary or secondary hypertension.

#### ECLAMPTIC UREMIA

The clinical picture of eclamptic uremia is characterized by signs of increased intracranial pressure, both general and localized. There are present headache, vomiting, slowing of the pulse rate, possibly

papillary edema or choked disk. They might be looked upon as premonitory of the eclamptic seizure. As silent premonitory signs there may be found increased knee- and ankle jerks, positive Babinski reflex and diminution of the abdominal reflexes. The eclamptic seizure does not differ from an epileptic convulsion. The picture might vary, reminding one of Jackson's epilepsy, especially in patients who for a long time have been lying on one side, resulting in cramps and paralysis confined to one side of the body. In patients who have been lying long on their backs, amaurosis may occur as a convulsive equivalent. The pale and puffy face empty of expression, the drowsiness and apathy may also be considered as premonitory symptoms. The stupor may change into coma without convulsions occurring. Maniacal excitement and other psychic disturbances may occur as equivalents or as after-effects of the last seizure with or without restlessness and jactation.

These phenomena may all occur without any impairment of kidney function and are usually absent in true uremia. The whole picture is to be correlated with edema of the brain or at least with a disturbance of the circulation in the brain.

At necropsy the brain is found edematous, pale and bloodless. The statement that cerebral edema is sometimes absent is difficult to check.

extremely  
and false

the brain. The latter can be recognized by a horizontal section through the brain *in situ* only, one then finds the brain filling the

had been pressed down into the foramen magnum. In such cases the lumbar pressure may not be elevated and lumbar puncture may endanger life. Gorke and Toppich<sup>10</sup> reported a case in which the initial pressure of the cerebrospinal fluid was 60 cm water. After a few cubic centimeters had been drained respiration stopped and death occurred. Necropsy revealed the brain pressed down into the occipital opening.

The interpretation of the eclamptic seizures being due to cerebral edema is supported by their occurrence in patients with Quincke's edema and normal kidneys. The author has developed the conception that cerebral edema is due to ischemic injury of the brain capillaries resulting from arteriolar constriction. He sees a support for this view in the fact that the eclamptic phenomena occur chiefly in patients with the pale form of hypertension and that a rise in arterial pressure usually precedes the eclamptic attacks. Other authors, e. g. Lichtwitz<sup>11</sup> and Oppenheimer and Fishberg<sup>12</sup> believe that the ischemia alone suffices to produce the eclamptic syndrome.

The last mentioned authors use the term hypertensive encephalopathy. Without denying that eclamptic phenomena might be

of the face and simultaneous eclamptic attacks or their equivalents were observed but elevation of blood pressure was absent, the fact that ingestion of water may precipitate eclamptic seizures that eclamptic seizures with practically complete success are prevented by withdrawal of salt and water that eclamptic manifestations disappear following administration of hypertonic solutions of magnesium sulphate intravenously by mouth or by rectum, all procedures which reduce the volume of the brain by withdrawing fluid from it and finally that in eclampsia gravidarum which the author considers as identical with eclamptic pseudouremia Zange-meister has demonstrated a very high intracranial pressure.

The author believes that in the presence of cerebral edema the onset of the eclamptic symptoms is facilitated by the active chemical mechanism of hypertension and we may believe that in the presence of cerebral edema the high blood pressure *per se* will increase the intracranial pressure pressing the brain against the cranial wall. It is however to be noted that Rowntree<sup>21</sup> succeeded in producing a marked increase in intracranial pressure and convulsions by continued ingestion of water alone.

In regard to prevention and treatment of eclamptic pseudouremia it should be recalled that Nonnenbruch<sup>17</sup> in 80 patients with war nephritis observed 16 instances of eclamptic convulsions. After the adoption of the hunger and thirst treatment Nonnenbruch saw only 1 instance of eclamptic uremia among several hundred cases and in this 1 case he found that the patient had secretly obtained enough fluid to increase his weight by 5 kg. Similar results are reported in regard to the prevention of eclampsia of pregnancy by the same treatment.

#### THE PSEUDOUREMIC SYMPTOMS OF CHRONIC HYPERTENSION

Symptoms in many respects similar to those encountered in acute

bulk of the symptoms we believe are correctly interpreted on the basis of ischemia or vasoconstriction and there may exist either a



## UREMIA

frequency to headaches and vertigo there occur transitory amaurosis hemiplegia aphasia astereognosis transitory monoplegia and hemiplegia and rarely epileptiform attacks.

As equivalents to the cerebral symptoms peripheral symptoms occur such as numb fingers intermittent claudication angina pectoris all signs of transitory interference with the circulation. Further one might have occasion to observe sudden elevation of the blood pressure with or without other symptoms conditions described by Pal<sup>1</sup> long ago under the name of vascular crises. Psychic disturbances of varying severity might develop occasionally resembling dementia paralytica. Finally we enumerate the most characteristic symptoms retinitis albuminurica paroxysmal dyspnea and Cheyne-Stokes respiration.

It may be accepted as certain that the transitory cerebral episodes and the psychic symptoms too are due to functional circulatory disturbances in the respective centers or areas. It is not settled whether within these centers or areas arteriosclerosis of the cerebral vessels is always present or whether a localized vascular spasm as suggested by Pal might occur even where there is no local disease. It is well known that we cannot predict the behavior of the arteries in hypertensive patients. They may show a reversed reaction after interruption of the circulation and respond not to normal arteries with dilatation but with continued contraction. Thus the angio-spastic insults may become the precursors of permanent lesions thrombosis or cerebral hemorrhage. (See below.)

The presumption of cerebral ischemia presupposes the active mechanism of pale hypertension and it will be of interest in the future to analyze the cerebral symptoms which occur in pale hypertension only and which may be found also in red hypertension. The one pathological process so far which occurs only in pale hypertension and definitely proves that in the mechanism of elevating the blood pressure we deal with a general vasoconstriction is retinitis albuminurica. This was formerly considered a sign of uremia. The author has shown that this important extrarenal symptom occurs even with fully preserved renal function without demonstrable renal insufficiency. It is not an azotemic retinitis as Hjal thought. Its occurrence is closely connected with an elevated blood pressure but rather with the vasoconstriction as the result of the hemogenous active mechanism of pale hypertension. It should be named *angio-spastic retinitis* rather than hypertensive retinitis. The retinal changes the author considers the result of the intense arterial ischemia. This concept seems important for the understanding not only of the retinal disease but of the renal change as well. If the histological changes of the retina which are the result of the angio-spastic ischemia are examined in detail

albuminuric retinitis most frequently and in its worst form. For a detailed discussion of the histology of the retinal changes, see Chapters XXXVII and XXXVIII.

Turning to the paroxysmal dyspnea occurring in hypertensive patients, two types, cardiac asthma and bulbar or cerebral asthma, must be distinguished having separate pathogenesis.

It is easy to correlate *cardiac asthma* with the failing of the left ventricle, but it is difficult to explain its paroxysmal and nocturnal occurrence when the patient is at complete rest while it is absent during the hours of the day when the demands upon the patient and upon his heart seem far greater. The author has observed that these attacks can be prevented with the accuracy of an experiment if no fluid intake whatsoever is allowed later than the preceding noon hour. He, therefore, sees in the nocturnal paroxysms an expression of the overloading of the weakened heart by the absorption of occult edema, facilitated by the recumbent position. This sudden influx of fluid is more than can be handled

might under similar circumstances promptly bring on an attack of cardiac asthma. Allowing the legs to hang down or, better, tying off the limbs often used with great success, throttles the afflux from the periphery, thereby diminishing the blood supply to the right heart. But these facts do not explain the inner mechanism of the paroxysmal dyspnea. If the left ventricle is failing while the function of the right ventricle is unimpaired or relatively less affected, an increased pressure in the pulmonary circulation must result. Thus an attack of cardiac asthma often leads to the production of pulmonary edema. Possibly the dyspnea is due to the increased pressure in the bloodvessels of the lungs. Some authors assume the dyspnea to be caused by an anemia of the respiratory center. But insufficient oxygenation of the blood in cardiac asthma has not been demonstrated.

Against the assumption of an anoxemia of the respiratory center speak the following clinical observations. The attacks of dyspnea will disappear if the power of the right ventricle decreases and edema develops or the attacks will cease if the patient spends the night in sitting position, thus allowing the occult edema in the lower part of the body to increase. The author, therefore, supposes that the increase of pressure in the pulmonary circulation might produce the dyspnea. It is characteristic of this condition that the insufficiency of the left ventricle is transitory and that the heart recovers,

if left alone, as soon as the excess of fluid in the vascular system has been disposed of in the form of abundant nycturia. The excellent response to dry food and rigorous salt restriction may even be looked upon as characteristic of the condition.

The second form of hypertensive asthma, the cerebral or bulbar form, is attributed to angiospastic disturbances of the blood supply to the respiratory center. One might figuratively speak of an angina or intermittent claudication of the respiratory center. Good oxygenation and aeration of the blood with a tendency toward alkalosis have been found (Straub and Meier<sup>20</sup>). It is difficult clinically to differentiate between cardiac and bulbar asthma. If at all, the difference would be made on the consideration that simultaneous pulmonary edema speaks in favor of the cardiac type, while a tendency toward periodic respiration speaks in favor of bulbar asthma.

That periodic or Cheyne-Stokes respiration is caused by disturbance of the cerebral or bulbar circulation may be considered as certain. But the condition is surprisingly complicated and there seems to be no escape from considering two etiologically separate groups.

In the first group the periodicity may be considered as respiratory or hematogenous such as is seen following upon an apnea voluntarily produced in a normal individual (Haldane and Poulton<sup>21</sup>) and also occurring on high mountains. It is caused by a lack of oxygen in the respiratory center and is characterized by the fact that the hyperpnea coincides with a stage of slowed pulse and low blood-pressure, the latter often rising during the apnea. In this condition the lack of oxygen in the blood becomes effective as a respiratory stimulus before the gradual rise of carbon dioxide begins to act as such. The rise of the blood-pressure appearing toward the end of the apnea is the result of anoxemic stimulation of the vasomotor center and ceases with the beginning of respiration. In this type of periodic respiration the respiratory center is leading.

The different relationship between respiration and blood-pressure forms the basis for distinguishing between the two groups. One may venture that in the second group the vasomotor center is leading. Here the hyperpnea coincides with the stage of high blood-pressure and the pressure falls in the breathing pause. This type occurs in hypertensive patients and in cerebral hemorrhage. According to the brilliant investigations of Naunyn and Schreiber,<sup>22</sup> as also of Cushing,<sup>23</sup> if the circulation of the vasomotor center is disturbed, a rhythmic rise and fall of the blood pressure results, the pressure rising with anoxemic stimulation. With improved oxygen supply the stimulus ceases the blood pressure drops until the deficient blood supply again acts as a stimulus of the vasomotor

center. With this cycle the respiration runs parallel increasing with rising and decreasing with falling pressure. A true apnea does not occur. Instead the breathing pause represents a real cerebral asphyxia during which along with the lowered pressure there may also be present miosis, adynamia, nystagmus, conjugated deviation, unconsciousness, even positive Babinski's reflexes (Tournay).

Normally the sensitivity of the respiratory center surpasses that of the vasomotor center and increases with decreasing arterial supply and *vice versa*. Not so in this group here the presumption of a decreased irritability of the respiratory center is inevitable. According to Schmidt<sup>22</sup> a reversal of the mode of normal reaction has taken place as the result of an advanced asphyxia of ganglion cells of the respiratory center. Therefore in this type of periodic respiration the breathing ceases with decreasing blood pressure until the asphyctic stimulation of the vasomotor center along with the rising pressure again restores the blood supply of the respiratory center and thereby its excitability.

An old observation by Elstein<sup>4</sup> is of interest. In a severely diabetic patient with periodic breathing Elstein observed the retinal arteries during the different phases of respiration. During the breathing pause the arteries were like thin threads visible only within the disk. With the return of the respiration they filled. In the same way we have to imagine the condition of the cerebral circulation in the second group of periodic respiration.

The frequency of irreparable cerebral accidents either by hemorrhage or softening among patients with chronic hypertensive conditions makes it logical to close with a consideration of the pathogenesis of cerebral hemorrhage. Here older opinions are undergoing radical changes. Rosenblath<sup>20</sup> expressed the original view contradicting former opinions that a lesion of the brain substance comes first and that a necrosis of the small arteries causes the hemorrhage secondarily. Rosenblath speaks of an unknown agent characterized by active chemical and enzymatic powers attacking a circumscribed region of the brain. This injury can have nothing to do with a general disturbance of metabolism or with renal function as Rosenblath believed but must be sought in a nutritional disturbance of a circumscribed area of the brain leading to injury and necrobiosis of cerebral tissue and liberation of substances injurious to the vessels. Thus the problem of cerebral

balance

The

blood

may precede an apoplectic stroke. (2) Quite similar hemorrhages

result from an embolus or thrombosis (3) The combination with Cheyne-Stokes breathing certainly resulting from insufficient blood supply to the bulbar centers frequently is present

The author believes that an asphyxia of the ganglion cells of the brain which are extremely susceptible to a lack of oxygen is responsible for the rapid decomposition products which paralyze the capillaries and cause necrosis of the small arteries. In this way are caused the hemorrhages in the perivascular lymph channels or false dissecting aneurysms and the necrotizing process progressing from the outside to the inside of the arteries (Stammier). Probably it is due to the special perivascular arrangement of the lymphatic channels in the brain that the injurious products and proteolytic ferments not only paralyze the capillaries but also injure the small arteries. The author is inclined to attribute the peculiar predilection of the basal stem ganglia for hemorrhages to their extraordinary sensitiveness to lack of oxygen. The fact that hemorrhages caused by carbon monoxide or cyanide poisoning have a predilection for the same regions also speaks for this conception.

Against the older view that the hemorrhage results from rupturing of arteriosclerotic vessels in consequence of high blood pressure the following observations might be noted. In the area surrounding the massive hemorrhage there are often multiple small hemorrhages (Rosenblith) or the massive hemorrhage itself is composed of innumerable small diplexetic hemorrhages (Schwartz) or besides the massive hemorrhage there are either widespread or symmetrical small hemorrhages in the stem ganglia on both sides of Westphal observed that in addition to the hemorrhagic area there were areas of white softening. Sometimes in apoplectic stroke follows a drop in blood pressure. Apoplexy also occurs in young hypertensive patients without arteriosclerotic or other organic lesions of the arteries all facts pointing against the correctness of the older views.

**Summary** — The eclamptic and pseudouramic phenomena may be termed acute and chronic false uremia. These phenomena may occur without renal insufficiency being present. They have a circulatory disturbance as a common pathogenetic factor. The circulatory disturbance may be generalized or localized permanent or transitory of sudden or insidious onset.

If the cardiovascular disturbance develops acutely changes in capillary permeability will predominate and a series of symptoms discussed above will develop on the basis of cerebral edema and increased intracranial pressure. Hydrostatic factors even under these circumstances influence the localization of the edema (anuria, hemipia, unilateral cramps, etc.). The cerebral edema depends on increased capillary permeability.

## TRUE UREMIA

(liquor diapedesis) The circulatory disturbance is caused by increased intracranial pressure pressing the brain on the rigid skull without the factor of cerebral vasoconstriction (eclamptic uremia in nephrosis)

If the cardiovascular disturbance develops gradually or to an extreme degree cerebral vasoconstriction will predominate. The variety of symptoms which may be interpreted as due to cerebral ischemia has been considered. The symptoms are not dependent on increased intracranial pressure but on vasoconstriction and may be brought about through general increase in vasotonus without arteriosclerosis as well as through localized arteriosclerosis without generalized vasoconstriction.

In the course of chronic hypertensive disease the two kinds of circulatory disturbance may merge. An increase in the amount and pressure of the cerebrospinal fluid may be present. Some of the symptoms of false uremia are of purely cardiac origin (cardiac asthma).

The cerebral circulatory disturbances may be augmented through water retention due to glomerular insufficiency.

A further connection between the eclamptic and angiospastic phenomena and renal function cannot be altogether neglected. The appearance of angiospastic phenomena including convulsions seems to be favored through renal insufficiency. Even so this does not necessitate the assumption of a retention of vasoactive substances rather of an increased production of such substances as has already been discussed in connection with pale hypertonia.

## TRUE UREMIA

When we compare the symptoms which appear only with renal insufficiency and which we have designated as symptoms of true uremia with those that occur in anuria we find them almost identical.

The essential symptoms are as follows: (1) General mental and bodily fatigue, weakness, drowsiness and a dulness which Vidal designated as veritable narcosis. (2) Excitation phenomena, muscular contractions, tendon jumping, an increase in the skin reflexes, narrowing of the pupils and deep breathing. (3) Rapid loss in weight and decrease in muscle mass. (4) Dyspeptic symptoms, loss of appetite, hiccoughs, vomiting. (5) Tendency to inflammation and necrosis, laryngitis, pharyngitis, stomatitis, gastritis, enteritis, necrotic ulcers of the mouth, stomach, intestinal mucosa and the skin and in addition pericarditis. (6) Drop in temperature.

(7) Odor of urine from the breath (8) Absence of convulsions and of headaches

The picture is always the same but not always equally complete. Some cases begin with an eruption like measles or scarlet fever which directs the attention away from the kidney. There are cases in which the dyspeptic symptoms are in the background and others where the diagnosis of uremia is missed because the dyspeptic symptoms dominate. In some cases the muscle contractions never occur. In other cases deep breathing predominates. Asthenia seems to be the most constant symptom.

**Uremia and Retention of Waste Products** — In true uremia there is isosthenuria without polyuria and a retention of urinary solids in the blood. The problem of the pathogenesis of true uremia lies in the correlation of the clinical symptoms and the lethal outcome with the retention of waste products in the blood. It once seemed attractive to explain the symptoms on the basis of the toxicity of the urine. The experiments of Brucke<sup>54</sup> and of the author's co-workers Hartwich and Hessel<sup>55, 56</sup> have shown that when the urine from one kidney flows directly into the blood through a uretero-venous fistula the animals die sooner despite the normally functioning second kidney than after bilateral nephrectomy. If the situation is complicated by previously producing a hydronephrosis of the kidney which is to be anastomosed to the vein jaundice and acidosis appear. The blood shows a marked increase in non protein nitrogen and a strong xanthoproteic reaction and the animals die despite the fact that the other kidney is normal. These results are difficult to interpret but it is safe to state that the animals do not die from an ordinary uremia. The so-called toxicity of the urine has been much discussed and the urinary colloids have particularly been indicted. Pribram suspected them to be highly toxic. This is not borne out by experiments by Hartwich and Kerger<sup>57</sup> who observed the effect upon the isolated frog's heart of urines and of artificial solutions of the same salt composition as the urines. They found no evidence of any toxic effect of the urinary colloids but regularly found the artificial solutions more harmful and are inclined to attribute most of the effects to the altered potassium calcium ratio. Nevertheless the old conception that the patient in uremia is urinating into his own blood cannot be maintained.

Urea was the first substance to be looked upon as the cause of uremia and there are series of investigations both for and against this conception. The author concludes that urea might cause the death of animals and that it might become more toxic with decreas-

blood. The urea concentration in the blood in renal insufficiency can be increased by giving urea without producing uremic symptoms and true uremic symptoms may develop without any change

of the blood. On the other hand decomposition of urea by bacteria will take place wherever tissues rich with urea come in contact with air or with the ubiquitous urea splitting bacteria. Thus necrotic ulcers may develop on the mucous membranes of the gastro-intestinal tract and in purulent pyelonephritis ammoniacal necrosis of the kidney may be found.

TABLE 84—COMPARISON OF THE CHLORIDE AND NON PROTEIN NITROGEN CONTENT OF BRAIN AND BLOOD IN NORMAL AND UREMIC ANIMALS  
(AFTER KERPÉL-FRÖNIUS AND LEÖVET<sup>42</sup>)

	Gray substance		White substance		Blood		Mean dura tion hrs
	Cl	NPN	Cl	NPN	Cl	NPN	
Mean values for normal	173	103	166	156	345	36	
Mean values following ureteral obstruction	93	395	187	307	303-363	203-206	67.5
Percentage change	+17	+147	+13	+94	-4	+646	
Mean values following ureteral obstruction and 10 gm urea	195	451	164	304		349	41.0
Percentage change	+5	+176	1	+133		+1080	
Mean values following ureteral obstruction 4 gm NaCl per kilo	422	191	259	165	670	73	27.7
Percentage change	+144	+17	+50	+6	+65	+103	
Mean values following ureteral obstruction 7 gm NaCl per kilo	445	100	318	155	657	25	0.5
Percentage change	+157	+4	+91	+1	+91		

Von Koranyi and Lindemann correlated uremia with changes in the osmotic pressure of the blood emphasizing that its molecular concentration might be increased so as to depress the freezing point to as low as  $-0.9^{\circ}\text{C}$  (Straub<sup>43</sup>). Munzer in this saw a general salt effect but the increase in osmotic pressure is almost entirely due to retention of the easily diffusible urea. It is conceivable that when the sum of the dissolved molecules reaches a certain height injury may be produced in the ganglion cells of the brain. Blum and his co-workers<sup>47-49</sup> have compared the chloride content



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of different organs including the gray and white brain matter in normals in uremia with and without nitrogen retention and in diabetic coma. In these pathological conditions they found an increase of the chlorides of the gray matter, which increase far surpassed the increases in the other organs. Kerpel Ironius and Levey<sup>55</sup> found that the length of life of rabbits which had been made uremic was shortened by sodium chloride and urea feeding. The accumulation of non protein nitrogen and chlorides was found significantly higher in the gray matter of the brain than in the white. This difference correlates with the higher water content of the gray substance. Table 84 shows the mean values and percentage increase of chlorides and non protein nitrogen for the blood the white and gray matter correlated with duration of experiment. It appears that death occurs independently of uremia as soon as the chloride and non protein nitrogen content of the gray matter has reached a value about 150 per cent above normal. Chabrier and Castro-Galhardo<sup>56</sup> see the essential sign of uremic intoxication in the increase in the non protein nitrogen exclusive of urea the residual nitrogen which shows a rapid rise during the final stage when uremic symptoms develop. It may be assumed that creatinine and perhaps also uric acid are not toxic.

TABLE 85.—CHIEF CONSTITUENTS OF PLASMA NON PROTEIN NITROGEN IN HEALTH AND RENAL INSUFFICIENCY (MG. PER 100 CC.) (AFTER BERGLUND<sup>57</sup>)

Twelve normal young men		Average	Less N	Creatinine	Less acid	Residual N	NPN
Minimum	Maximum						
Average		4.3	9.6			1.8	19.0
Renal insufficiency 7 instances		6.2	17.3			11.5	36.0
		5.3	10.4			6.7	24.7
1		4.3	13.0	1.8			
2		5.6	47.0	2.3			
3		3.5	52.0	3.0	3.7	20.0	39.0
4		5.4	71.0	8.1	6.4	18.0	40.0
5		6.2	109.0	8.1	6.6	18.0	7.0
6		7.6	214.0	14.5	9.3	21.0	103.0
7		7.3	234.0	19.2	18.4	23.0	144.0
					21.0	52.0	293.0
						51.0	306.0

Representative examples of the concentration of the most commonly determined constituents of the non protein nitrogen in normals and during different stages of retention between the concentrations given in Table 85. A comparison between the concentrations of the same compounds in plasma and cerebrospinal fluid is given in Table 86. It will be observed that the residual nitrogen does not pass into the cerebrospinal fluid. Looking upon the nitrogen reten-

tion from the viewpoint of increased molecular concentration we remember that the urea nitrogen represents a urea concentration of a little more than double the nitrogen and that the urea concen-

much as the urea nitrogen. To this has to be added a further retention of nitrogen-free protein derivatives which will be considered later. The molecular concentration of these compounds is not known.

TABLE 86—NON PROTEIN NITROGEN DISTRIBUTION BETWEEN PLASMA AND CEREBROSPINAL FLUID (MG PER 100 CC) (AFTER BERGLUND<sup>45</sup>)

Condition	Amino-acid N		Urea N		Creatin <sup>100</sup>		Uric acid		H <sup>2</sup> actual N		NPN	
	Cerebrospinal fluid		Plasma		Cerebrospinal fluid		Plasma		Cerebrospinal fluid		Plasma	
	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid
Non nephritic Uremia (Case 6 Table III)		2.0		11		0.9		0.8		3		17
Uremia (Case 7 Table 83)	7.5	2.8	214	218	14.5	6.1	19.4	4.5	32	0	285	222
Same 24 hrs later	6.7	2.6			22.0	6.3	22.6	2.0			324	235
	7.1	3.0		272	21.3	8.5	20.6	2.0			345	279

In uremia the products of protein putrefaction in the intestines are increased in the blood. Obermayer and Popper noticed the odor of the serum in uremia and the author has observed fecal odor from the distillate of uremic blood. The serum odor might be

test, originally making use of a strong ammoniacal reaction for the development of the characteristic color, through the work of Pauly<sup>79</sup> and others now may be interpreted as a test for uremia.

reported by Decker<sup>12-14</sup> on uremic sera concern themselves with this reaction. (2) In the second diazo reaction in use, known by Ehrlich but commonly connected with the name of Hujmans Van

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den Bergh, the color develops in strongly acid solution. This reaction seems to be specific for bilirubin. (3) The third reaction\* is the one related to uramic conditions. It was described by Andrewes<sup>4</sup> as a two-phase reaction, the first phenomenon being the development of a brown buff color which on careful alkalization passes through a characteristic pink or cherry-colored stage. Harrison and Bromfield<sup>5</sup> have made it almost certain that the reaction is due to indican or possibly in part to indoxyl glycuronate. Chrometzky<sup>6</sup> independently described the first step of the reaction. Though the reaction has been found positive in uremic sera only, and runs roughly parallel with the accumulation of urea, it does not give the same information as to impending danger as the reaction to be discussed presently. Indican does not pass into the cerebro-

\* *The Diazo Test for Renal Insufficiency (Simplified Method)* — Reagents (identical with those used in Van den Bergh's test)

Sulphanilic acid  
Concentrated hydrochloric acid  
Distilled water

## Solution A

1 gm  
15 cc  
to 1000 cc

## Solution B

0.5 gm  
to 100 cc

Sodium nitrite  
Distilled water

The diazo reagent is prepared by mixing 25 cc of Solution A with 0.75 cc of Solution B. The mixture may be kept for at least a week at room temperature without loss of sensitivity so far as Andrewes' reaction is concerned although of course the Solutions A and B must be mixed freshly for use in the Van den Bergh test. The mixture often turns slightly yellow after keeping for a day or two but this does not matter in Andrewes' test.

Serum or oxalated plasma is obtained from the patient in the usual way. To 1 volume of serum 2 volumes of alcohol absolute or 96 per cent are added. The precipitated proteins are separated by centrifuging or filtering. A slightly improved extraction may be obtained by heating the mixture of serum and alcohol to the boiling point. To 4 volumes of the filtrate 1 volume of the diazo reagent is added. The mixture is boiled thoroughly for one half to one minute and a solution of 20 per cent sodium carbonate is added drop by drop shaking after each addition. The alkali may be added immediately after the boiling.

On boiling the mixture of protein free filtrate and diazo reagent a yellow brown or buff color always results in positive cases but a similar color may also be obtained in negative cases. The color change on alkalization is the essential part of the reaction. The test should be called positive only when a definite pink or cherry red color is seen. This pink color is fleeting. It may last for a few seconds only and the mixture must therefore be observed carefully while adding the sodium carbonate. In a very few severe cases of uremia the pink color may persist for longer periods even up to one-half hour. The volumes recommended may be judged sufficiently well by eye without greatly lessening the sensitivity of the reaction.

Substances other than that responsible for Andrewes' reaction may give a yellow brown color at the first stage (in acid solution) but these other substances do not yield a red color on alkalization. (Harrison G. A. and Hewett L. F. Brit Med J p 1139 1927)

*The Xanthoproteic Reaction on Blood and Other Body Fluids* — A 1 to 1 protein free filtrate with 20 per cent trichloroacetic acid is prepared. To 2 cc filtrate is added 0.5 cc concentrated HNO<sub>3</sub>; the solution is heated one half minute cooled and 15 cc of 33 per cent NaOH is added. A yellowish brown to reddish brown color indicates a positive reaction. (Becher E. München med Wchnschr No 46 1914)

spinal fluid There are reasons to look upon indican and its mother substances indol and indoxyl as relatively non toxic

TABLE 87—CORRELATION OF UREMIC SYMPTOMS WITH XANTHOPROTEIC REACTION AND UREA CONTENT OF THE BLOOD (BECHER AND KOCH<sup>43</sup>)

	N P N	Urea	Ind an	Xantho- proteic	Ure acid	Remarks
Feb 16	194	213	+++	83	7.8	Definite uremic symptoms
0	136	224	++++	140	7.6	Vomiting muscular contractions
21		234	++++	130		Condition getting worse
25		195	++++	112	8.9	Disappearance of uremic symptoms
Mar 4	190	407		73		Condition becoming better
9	110	193	+++	60		Daily 50 gm. of urea.
12	129	233	++++	42		Subjectively feels well
16		421	+++	46		No uremic symptoms
April 14	132	232	++++	50		Symptoms of true uremia

The author believes a different situation to prevail in regard to the phenol derivatives. In his experience no blood test gives a better basis for prognosis in renal insufficiency than Becher's xanthoproteic reaction which informs us as to the degree of retention of aromatic substances in general. Table 87 gives a characteristic example taken from the publication of Becher and Koch<sup>43</sup>. In this case the symptoms and signs of uremia increased up to February 20 and death was expected. At a urea value of 224 mg. per 100 cc. the xanthoproteic value reached its highest point of 140. Contrary to expectation improvement took place and with disappearance of uremic symptoms the xanthoproteic value fell to one-half, whereas the blood urea remained the same. From March 9 urea was given until the blood urea reached 420 mg. The xanthoproteic reaction fell to 42 and to 46 scale divisions and the patient felt well.

toms of uremia recurred although the urea had dropped from 420 to 232. This case proves that the uremic symptoms do not parallel the retention of urea but rather the aromatic substances in the blood. Symptoms of uremia develop at colorimetric xanthoproteic values of 100 (normal up to 25 in Becher's technique).

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rabbits they survived the operation ten hours. The animals produced a water-clear urine free from phenols in bean and urechro-

gen and following extirpation of the kidneys no indican was found in the blood. The author has observed among the large number of nephropathies in his clinic in Halle and Frankfurt not a single instance of true uremia without elevated phenol values or a strong qualitative xanthoproteic reaction. Becher's findings of phenols in the blood in severe renal insufficiency and uremia is of pathogenetic significance. Whenever it was possible through dietetic and charcoal treatment to free the blood of phenols improvement occurred and uremic symptoms disappeared. Becher points out that the symptoms of uremia—fatigue, insomnia, loss of weight, gastro-intestinal symptoms, vomiting, drop in temperature, skin symptoms, cachexia—remind one of the symptoms seen when the carbolic acid spray was used by surgeons and of the symptoms found among workmen in carbolic acid factories. Perhaps the final decrease in kidney function might be explained by injuries due to phenols. Like Becher the author is not prepared to regard uremia as a simple phenol intoxication.

Though the practical value of the xanthoproteic reaction is well established the present shortcomings of the test shall not be left out of consideration. Being chiefly a qualitative test the estimation of the strength of the reaction is only roughly quantitative which indeed is natural as long as the compound or compounds responsible for the reaction remain unknown. Since all aromatic substances react positively the identification is not easy. Becher so far has found that the substances responsible for the reaction are thermostable and that there is no significant increase in color after hydrolysis that the substances are partly volatile and partly ether soluble. From this Becher assumes the following compounds to participate in the reaction: phenols, mostly conjugated dihydroxyphenols and oxyacids. The oxyacid fraction (the portion of reacting bodies extractable by ether) in 1 instance showed an increase of forty times the normal (Becher, Doenecke and Latzner).

To what extent these compounds or others that might participate in the reaction are of intestinal origin or products of intermediary metabolism cannot be judged at present. Neither is any definite knowledge possessed as to their respective toxicity. Becher, however, made the important observation that in true uremia a part of the phenol bodies is in a free and therefore non-detoxified state in the blood. They are much more highly toxic than the bound phenols. The appearance of these undetoxified products of intestinal decomposition depends upon the fact that the processes are no longer

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may be noted. In contrast to the behavior of urea the results a still further observation of the

decomposition products do not ordinarily diffuse into the cerebrospinal fluid. Their first appearance in the cerebrospinal fluid coincides with the onset of the uremic symptoms and indicates that their penetration to the central nervous system is the vital factor in the production of true uremia.

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retained in the blood and in the skin. They probably have not the toxic effects assumed by Thudichum. The chromogens retained in the skin may go over to the colored compounds themselves by the action of light and the water-clear serum and the colorless urine

of the uremic picture to the retention of products of intestinal putrefaction. So far the xanthoproteic reaction which perhaps chiefly depends upon retention of such products is the only chemical reaction of the blood which runs parallel with the degree of uremic intoxication. It should not be forgotten that the classical experiments of Magnus Alsleben have shown that the intestines represent the greatest source of toxins in the organism.

**Uremia and Acid Intoxication?** (Straub and Schlaver).—It is well known that acidosis in renal insufficiency may reach a degree incompatible with life but even if less developed it is an obligatory symptom in true uremia. The severity of the acidosis sometimes

is present for several days before coma develops.

Different possibilities have been considered for the cause of

1. Abnormal production or retention of organic acids. After complete analysis of the altera-

questions formulated except possibly to rule out the role of decreased ammonia formation. If the acidosis were founded upon a dis-

turbed formation of ammonia all nephritics would remain free of uremic acidosis on a basic diet. It is also not possible to explain the renewed development of acidosis after administration of large amounts of alkali on the basis of deficient ammonia formation

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requisites for a solution accurate methods for the needed analyses and an understanding of the mechanism of the normal acid base balance are now on hand. To facilitate the discussion the reader's

attention is called to the normal acid and base composition of the plasma as given in Fig 150. With the help of the figure the acidosis in severe renal insufficiency and coma might be discussed. A great number of workers have contributed to our knowledge in this field. The data of Palmer and his co-workers, Peters and his staff<sup>79, 80</sup> and Henderson<sup>74, 75</sup> and his group will particularly be considered.

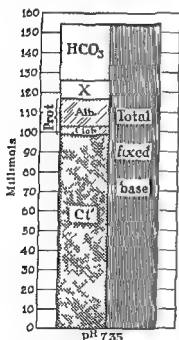
With the commonly used definition of acidosis bicarbonate deficiency is nearly always found. The plasma  $\text{CO}_2$ , normally present in an amount to combine with approximately 20 per cent of the total base, may become reduced by four fifths of its normal value.

The chlorides normally present in amounts equivalent to approximately 66 per cent of the total base may be either increased or decreased, which latter condition is the more commonly observed

FIG 150 — Acid base composition of normal plasma

and almost the rule in extreme acidosis. The negative variations may reach values 20 to 30 per cent below the normal and are often of greater magnitude than the positive ones. The decrease is independent of the presence of edema and is the first example of

to characterize as  
low chloride level  
greater than would



due to a decrease of the chlorides, into the total base, so of

reduced and never increased—the plasma proteins. Normally the plasma proteins have been calculated probably with high degree  
 80 per cent of the total  
 than three fourths

With the reductions (see Chapter XXX) the base binding capacity will diminish. Peters has calculated that reductions of 50 per cent and more may be found. As the acidosis reaches a degree sufficient to shift the pH toward 7, a further reduction of the proteins' acid role in the plasma takes place.

The three acid components of the plasma just discussed normally are equivalent to about 95 per cent of the total base. So far in nephritic acidosis they have all been found decreased in numerous instances at least. The cause of the acidosis thus might be found either in an increase of acid radicals not yet considered or in a decrease in the fixed base.

The convenient and accurate determination of the total fixed base has made it unnecessary longer to rely upon the summation of the separate bases in which the determination of the biggest factor the sodium was uncertain at its best. The total base concentration is one of the least variable among physiological constants (154 millimols) and normally is chiefly responsible for the constancy of the osmotic pressure. In nephritic acidosis any type of variation in total base may occur: it is seldom increased but often decreased to as low as 130 millimols or lower. With such reductions there would normally be a lowered osmotic pressure, but even taking into account the intricacies of cryoscopy when applied to blood serum it might be accepted as established that the osmotic pressure in nephritic acidosis may be normal or increased because of retention of non-electrolytes, particularly urea, which may reach a level of 50 to 70 millimols or more (100 mg. urea nitrogen being equivalent to 35 S millimols).

There is no satisfactory explanation for the base diminution. If attracted by teleological viewpoints it might be inquired whether

relation with the coexistence of edema such an assumption would



necessitate another one, the so-called dry retention of electrolytes. Though invitations to accept such a concept by no means have been wanting, particularly from French clinicians its existence has never been indisputably proven. Another explanation might be sought

ized in the kidney and, as a matter of fact, cannot possibly be localized in the kidney alone, considering what is known about the function of the intestines in this respect. That the kidney plays an important rôle in base preservation cannot be doubted, particularly in light of the new concept of ammonia formation introduced by Nash and Benedict. Thus, as a tentative explanation of the characteristic cation deficit in severe renal insufficiency, there

others than the ones already dealt with. In balancing acid and base equivalents normally there is but a small acid fraction left, obtainable by difference only. The experimental errors affecting

acidosis though both are said to be elevated in severe renal insufficiency. The remainder represents undetermined organic acids. In nephritic acidosis  $\Sigma$  is usually increased, frequently doubled and not very seldom tripled with values calculated as 30 to 50 millimols, as high as in diabetic coma.

With a twentyfold increase of non protein nitrogen including 50 mg. residual nitrogen representing unknown metabolites with strongly positive xanthoproteic and diazo reactions, indicating retention of aromatic substances, with undetermined acids in amounts corresponding to 50 millimols, with the osmotic pressure raised by one-third and the concentration of hydrogen ions increased nearly three times, with the patient comatose, laboring with Kussmaul's breathing a stage has been reached where all physiological regulations are on the verge of complete breakdown.

To select from this picture the symptoms which are of renal origin and those which are not is impossible. That the renal path-

\* MacNider\* in animal experiments studied both functionally and histologically the effects of acid and alkali. As is the case in diabetic coma, so id material dogs with acid effects biology the effects upon

ology plays the most important rôle is clear, but, to quote Henderson<sup>21</sup> "It is manifestly impossible to regard the changes in the blood as direct effects of the pathological state of the kidney. On the contrary, nothing could be clearer than that a disturbance of the whole organism exists. This involves adjustments and readjustments between all the parts and at this stage the breaking-point has been reached. There can be little doubt, for instance, that the blood must exert harmful action on the kidney, which is hardly less than that exerted by the kidney on the blood. A similar statement will hold good for the heart and the other organs."

A problem as important as it is difficult is the identification of

of an aliphatic acidosis. With his co-workers the author has found the aliphatic ketone bodies missing in uremia, neither have we found increased amounts of lactic acid. In line with Becher's work we are inclined to look upon  $\lambda$  as partly made up of aromatic oxyacids, we are as a matter of fact, speaking of an aromatic acidosis of nephritis in contradistinction to the aliphatic acidosis of diabetes.

More recent investigations of Becher, Enger and Herrmann<sup>24</sup> have demonstrated that the acids which are present in the blood in true uremia belong to the group of organic ether soluble acids. Becher and his co-workers showed by direct isolation and quantitative determination of the ether soluble fraction that, estimated indirectly, these acids are sufficient to account for the anion deficiency. The acids are partly of aliphatic, partly of aromatic nature. Part of them are volatile with steam distillation part of them not. The author hopes to be able further to build out this structure with evidence not only of an intestinal origin as already considered but of a metabolic origin of these acid products of protein katabolism. The old, once almost discarded idea about toxic protein decomposition may once more find itself reinstated on the strength of new experimental evidence.

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## CHAPTER XL

### TREATMENT OF ACUTE DIFFUSE GLOMERULO- NEPHRITIS.

By FRANZ VOLHARD, M.D.

**Introduction — The Problems Involved in the Treatment of Acute Glomerulonephritis** — To the practising physician one of his most important tasks is the treatment of acute diffuse glomerulonephritis. It imposes a great responsibility but may also bring the greatest satisfaction.

The problem consists in the treatment of the acute stage of the disease.

irreparable organic changes in the kidney, i.e., in the glomeruli or the renal arteries or arterioles, for these organic changes in glom-

For the understanding of the dangers it is important to bear in mind that the true process consists in a general and also a renal vasoconstriction. Thus in the acute stages we are dealing with a functional condition which endangers not only the kidney but also the other organs, especially the central nervous system, and greatly threatens the heart. In the acute stage it is the danger to the heart which is of first and highest importance. The danger to the brain is second and to the kidneys only third. The danger that the functional condition in the kidneys will lead to lasting and irreparable changes increases with the degree and duration of the general vasoconstriction manifesting itself by hypertension. The hypertension, caused by spastic narrowing of the small peripheral arteries may set in suddenly, even over night. This means an enormous overload for the heart. The increased work can be accomplished only if the muscle fibers of the heart are stretched more than under normal conditions (Fick and Frank's law). The distention occurs automatically through an increase of the residual blood in the heart chambers due to the overload. A certain degree of dilatation of the heart thus is a necessary condition for increased work but includes a danger of overdistention.

The clinical picture of acute diffuse glomerulonephritis, therefore, may present itself in the form of an acute and most severe insufficiency of the heart with dyspnea of the highest degree, increase of the venous pressure and swelling of the liver. Almost every case that dies in the acute stage of the disease dies of cardiac insufficiency through overdilatation. This is very clearly recognized at necropsy. It is the danger which has to be avoided by all possible means. For this reason it is important (1) to keep the patients strictly in bed and (2) to relieve the overtension of the cardiovascular system. In critical instances the latter is accomplished by venesection but if time permits, complete restriction of fluid intake will suffice. The effect of such simple procedures is often astonishing. In a single day the clinical picture may change completely, and dyspnea may disappear. One must not be misled by a full and regular pulse. It is important to realize that a slow pulse belongs to the picture of acute diffuse glomerulonephritis. A rate of 80 is too high and a sign of imminent danger. Prompt use of heart stimulants is indicated as soon as the pulse goes beyond 50 to 60. Digitalis should be given in every such case. The promptest result is obtained from intravenous injection of strophanthin in doses of 0.3 mg., given once or twice a day in the beginning until the pulse rate comes down.

The second grave danger consists of cerebral edema, causing the convulsions of the so-called eclamptic uremia. This picture of so-called eclampsia, or convulsive uremia, has nothing to do with the true uremia caused by renal insufficiency. Convulsive uremia consists of increased intracranial pressure and the equivalent utterances of it are headache, vomiting, apathy, somnolence, amaurosis (See also Chapter XXIX). The higher the blood pressure, the greater the danger. The energetic relief of the convulsions is given by intravenous injection of castor oil or magnesium sulphate according to Blackfan.

The third danger is that of urine intoxication which threatens in acute stages only in cases of anuria or very marked oliguria. In such instances surprising results have at times been seen with prompt recovery after decapsulation of the kidneys. The author has observed such cases though in other instances there has been no improvement. Roentgen ray treatment is reported as having given good results in some cases so has splanchnic anesthesia. The secret of the results seems to lie in an improvement of renal circulation, as shown by Hulse and Litzner in animal experiments. In

severe cases with anuria persisting over several days denervation

e power of

Usually  
diuresis sets in with the relief of the circulatory overtension through  
venesection or absolute restriction of fluid intake and is favored  
by diathermy of the kidney region twice daily

The prevention of danger to the heart brain and kidneys in the  
acute stages are best affected by complete abstinence from food and  
drink--the so-called hunger and thirst treatment. The author  
allows the patients to lie hungry and thirsty for three four or more  
days by all means until diuresis and fall in blood pressure and  
weight are noticed. The edema as a rule disappears promptly  
the more promptly the earlier the patient comes under treatment.  
The dyspnea and with it the danger to the heart diminishes the  
pulse slows down the body weight decreases and the edema may  
disappear even if the urinary volume does not increase. As to the  
technique of the hunger and thirst treatment it should be men-  
tioned that first of all the bowels should be thoroughly emptied.  
In children and weakened patients the starvation treatment might  
be made milder and acidosis prevented by offering fresh fruit  
cracker potato or sugar water in small amounts or by intravenous  
injection of hypertonic glucose solution.

The second part of the author's treatment consists in what he  
calls *Wasserstoss* or the dilution test. In case the blood pressure  
has somewhat decreased and the urinary volume increased after  
the period of hunger and thirst he makes the water test with 3 pints  
(1500 cc) of weak tea early in the morning to be taken in the  
course of one-half or three-quarters of an hour. Very often this  
leads promptly to a surprising diuresis a draining off of edema and  
a distinct decrease of the blood pressure. One cannot escape the  
impression that the sudden flooding by the water intake favors the  
restoration of renal circulation and accelerates the recovery. It is  
noteworthy that the same amount of fluid taken in divided doses  
during the course of the day has not nearly the beneficial effect of  
this large single dose which is able to produce a marked outflow of  
urine. In case the water test is ineffective it may be repeated after  
two or three days during which time the patient receives a salt free  
diet without fluids. A diuretic such as theojellin is given with the  
second water intake. The *Wasserstoss* is repeated until the blood  
pressure returns to normal.

**Criteria of Recovery** The result of the treatment is judged by  
1) the amount  
Part  
2) the

measuring of the blood pressure twice a day



*ACUTE DIFFUSE GLOMERULONEPHRITIS*

Recovery from diffuse acute nephritis should be spoken of only when the blood pressure has permanently come down to normal levels or lower

**Importance of Early Treatment**—For the success of the treatment the most important factor is that of time. Every day that a patient walks about without having his condition recognized renders the prognosis darker and diminishes the chances of complete ultimate recovery. All of our adult patients who have come to the clinic in the first weeks of the disease have completely recovered. For this reason a prompt recognition of the condition, the early diagnosis of the acute diffuse glomerulonephritis, is of prime and foremost importance. Not every case of nephritis starts with the clinical symptoms of acute cardiac insufficiency and dyspnea. There are cases of slow development wherein the patient complains only of fatigue or headache or loss of appetite or even of nothing at all. It is therefore necessary to watch for nephritis after acute tonsillitis and other infections just as we are accustomed to do after scarlet fever. And we have to watch for it not so much in the acute stage of these infections as during the first two weeks following the fever.

# CHAPTER XII CENTRAL SYMPTOMS IN ACUTE GLOMERULAR NEPHRITIS AND THEIR TREATMENT

By KENNETH D. BLACKFAN, M.D.  
AND  
ILLIAN M. BUTLER, M.D.

**Introduction**—Recent clinical classifications of Bright's disease by Addis, Van Slyke, Aldrich, and Blackfan and McKhann<sup>1</sup> are generally enough used and clearly enough compared to Volhard and Fahr's<sup>2</sup> pathological classification to make an elaboration on the terminology of classification of nephritis in children unnecessary. The forms of Bright's disease encountered in children are approximately the same clinically and pathologically as those found in adults but they differ materially in their frequency of occurrence. Arteriosclerotic Bright's disease is the common form in adults and in other types in this age group the chronic forms predominate and are often complicated by cardiovascular changes. In children the great majority of cases are acute hemorrhagic Bright's disease. Structural cardiovascular changes occur but seldom and arteriosclerotic Bright's disease is rarely encountered. There is in addition a rare disease peculiar to the younger group usually designated as congenital interstitial nephritis or renal rickets.

In this chapter the authors wish to consider acute hemorrhagic nephritis as it occurs in children. For the pediatrician it is particularly important as it constitutes approximately 5 per cent of the cases of nephritis occurring in the age group with which he is concerned. Secondly, there is a very definite syndrome which is about 8 per cent of the cases culminates in death unless the progress of the syndrome is checked by therapy which has been shown to be specific and peculiarly effective.

**Course of the Disease**—The usual case follows an upper respiratory infection by an interval of one to three weeks. Puffiness is noted about the eyes. The urine is bloody and scanty sometimes to the point of anuria and of high specific gravity. Pallor appears and the appetite suffers. The albumin and sediment are as given by Addis in acute hemorrhagic nephritis. Blood analyses may show though not necessarily high values for nitrogen. Then in certain

cases central nervous system symptoms ensue. These are headache, visual disturbances, or frequently a slowing of convulsions and coma, the name pseudo or convulsive uremia. To them are attributed the fatalities in the acute stage of this disease.

Edema is present. It is not the marked pitting edema of nephrosis or the later stages of glomerular nephritis. It gives one the impres-

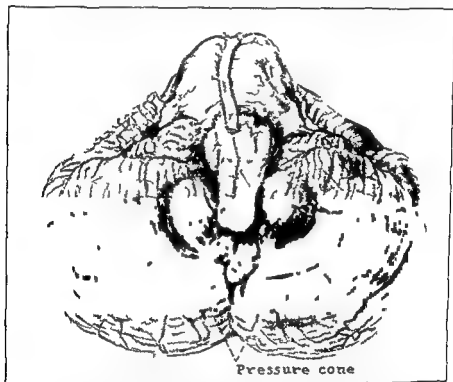


FIG 157 — Medullary cone phase: compression of medullary structures, flattened convolutions and sphenoid. (Oxford Medicine, courtesy of the Oxford Univ. Press.)

sion of being intracellular, not the shifting intercellular edema of subcutaneous tissue spaces and body cavities. This differential type of edema exists in the brain. The optic disks may show papilledema. The brain is firm. It weighs 25 to 30 per cent more than is normal for the age. The dura is tense, the convolutions are flattened, and the ventricles are compressed to appear nearly as slits when the brain is sectioned. There is every indication of the rapid development of increase in the volume of the brain with

increased intracranial pressure. Figure 155 shows the medullary cone phase with the medulla compressed into the foramen magnum.

The blood pressure is elevated or is rapidly rising. The rapidity of the rise is of as much importance as the actual height. The amount of blood in the urine and the retention of nitrogenous substances are not reliable indices of the severity of the condition. The evidence of impending cerebral symptoms is best indicated by the course of the blood pressure and the degree of oliguria.

Whatever the major cause, clinical experience shows that the rise in blood pressure parallels the severity of the cerebral symptoms. A fall in blood-pressure alleviates them. Possibly the same is true of intracranial pressure. The beneficial effects of the withdrawing of spinal fluid argue for such a view. Certainly intracranial pressure is elevated with the presence of these symptoms. But the evidence concerning the course and actual height of the intracranial pressure is not clear because of the difficulty of obtaining reliable measurements. Sometimes very little fluid can be obtained by lumbar puncture and in the procedure there is the danger of incarceration of the edematous brain and compression of the medulla. The evidence is clear as regards blood pressure, its course is easily followed and means of lowering it are free from danger. In the treatment developed by one of the authors and discussed in the following paragraphs attention has been focussed on the blood-pressure.

**Magnesium Sulphate Therapy**—Some years ago, Fisher<sup>4</sup> demonstrated that the blood pressure in acute nephritis could be lowered by the intravenous injection of a hypertonic salt solution consisting of 10 gm  $\text{Na}_2\text{CO}_3$ , 10H $_2\text{O}$  + 14 gm  $\text{NaCl}$  per liter of water. Sub-

sequent work by Black et al.<sup>5</sup> has shown that the physiological action of  $\text{NaCl}$  and  $\text{MgSO}_4$  are such as to indicate the use of the latter salt. The  $\text{NaCl}$  solution

such retention follows  $\text{MgSO}_4$ . The importance of the Na ion in water balance would lead one to expect this. With the existence of cerebral edema the authors prefer to avoid the employment of a sodium salt.

In order to prevent the necessity of repeated intravenous injections magnesium sulphate is given by mouth and rectum to such extent as to cause catharsis. The dose is 1 to 2 ounces of 50 per cent  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  every four hours. This is effective in preventing a

subsequent rise in blood pressure and is an important part of the treatment. Indeed, in mild cases such oral and rectal administration is alone an efficient means of preventing the development of cerebral symptoms.

As an illustration of the course and treatment the case from which Fig 159 was taken is quoted

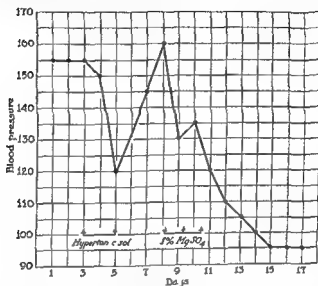


FIG 158 —Effect of hypertonic salt solution and 1 per cent  $MgSO_4$  intravenously on blood pressure

The patient D. E. and her husband were admitted to the hospital with

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subsequent

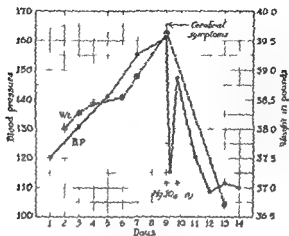


FIG 159 —Acute hemorrhagic nephritis with cerebral symptoms the effect of  $MgSO_4$  on blood pressure and weight

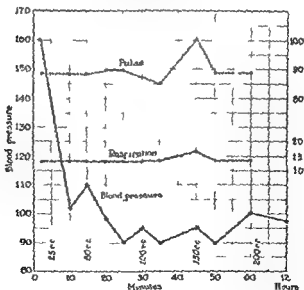


FIG 160 —Immediate effect of intravenous  $MgSO_4$  on blood pressure pulse and respiration

Figure 160 shows in detail the effect of magnesium sulphate intravenously on blood pressure pulse and respiration

Blackfan and McKhann<sup>2</sup> have introduced intramuscular injection of magnesium sulphate instead of the intravenous method of administration. The dose by this route is from 4 to 10 cc of a 25 per cent solution of  $MgSO_4 \cdot 7H_2O$ . If the blood pressure does not fall the injection is repeated (Fig 161)

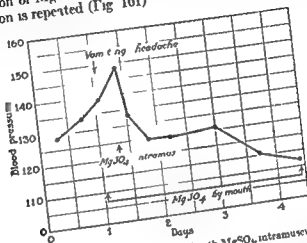


FIG 161 — Acute hemorrhagic nephritis treated with  $MgSO_4$  intramuscularly and by mouth

In using magnesium sulphate as outlined above, toxic symptoms are not encountered but one should know, when using it in this manner the symptoms of overdosage. The particularly important symptom is alteration in respiration at first a slowing and irregularity and then cessation. Five to 10 cc of 3 to 5 per cent  $CaCl_2$  solution intravenously is the antidote.

**The Physiological Action of Magnesium Sulphate** — Such are the empirical facts. At the present time we cannot be sure of the explanation.

Meltzer,<sup>33</sup> in using magnesium sulphate in the treatment of tetanus and as an anesthetic ascribed its action to a synaptic inhibition to the passage of nerve impulses. To be sure, his doses were usually larger than the doses given here and perhaps it is not fair to suggest a similar physiological action. Yet he cites a case of tetanus in which 10 cc of a 25 per cent solution were given intramuscularly every six hours, and he produced anesthesia in 1 case by giving 180 cc of a 6 per cent solution to a man of 160 pounds. Reduce this to the 40 pounds of a child and we find it equivalent to 135 cc of 2 per cent  $MgSO_4 \cdot 7H_2O$  or 1 per cent  $MgSO_4$ . But even should some such narcotic effect be present, it seems certain that this cannot account for the entire picture.

Lazard<sup>7</sup> in the treatment of eclampsia uses 20 cc of 10 per cent  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  repeating the dose usually every twelve hours. This is very similar to the authors dosage. He ascribes the beneficial effect to reduction of brain volume and intracranial pressure. He does not state whether the effect is a primary reduction of intracranial pressure or a secondary effect following the lowering of the blood pressure.

Clinical evidence favors the view that increased intracranial pressure is the cause of the elevated blood pressure. But it seems justifiable to question the possibility of intracranial pressures in nephritis sufficiently high to cause the observed elevations in blood-pressure. Experimentally it requires an intracranial pressure of at least 800 mm. of water to produce such elevations in blood-pressure. Available data would lead one to believe that such pressures are not attained in acute nephritis. Against this argument the point has been made that the observed spinal fluid pressures may not correctly indicate the intracranial pressure, the latter being high possibly interferes with the free passage of fluid.

Fisher ascribed the beneficial effects of his solution to its alkalinity and hypertonicity. His views concerning the alkalinity do not seem tenable. Of course his solution is hypertonic (0.27 molar) and if its action is due to an osmotic effect would tend to reduce the cerebral edema. Weed and McKibben<sup>12</sup> believe that the reduction of brain volume following the injection of a hypertonic salt solution is due to such osmotic action. But one encounters considerable difficulty in estimating the osmotic action of a bivalent salt such as magnesium sulphate. Calculated on a molar basis it is hypotonic, calculated on the basis of ionic strength it is probably hypertonic. Further it is known from the effect of magnesium salts on the solubilities of other salts and proteins that the magnesium ion has a unique action. At the present time it seems that the way in

not shown constriction though the retinal veins have been congested. But should there be a capillary constriction particularly if more generalized than a constriction of the renal vessels that in itself might be the primary cause of the hypertension with cerebral edema a secondary sequence. Possibly magnesium sulphate acting as a capillary dilator effects the blood-pressure and thus the cerebral symptoms.

Presumably the oral and rectal administration of magnesium sulphate is effective through the dehydrating action.



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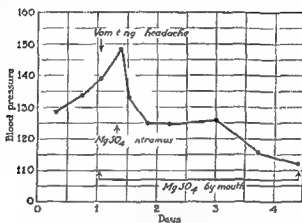


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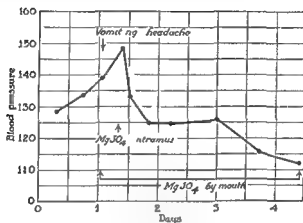


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muscularly every six hours, and he produced anesthesia in 1 case by giving 180 cc of a 6 per cent solution to a man of 160 pounds. Reduce this to the 40 pounds of a child and we find it equivalent to 135 cc of 2 per cent  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  or 1 per cent  $\text{MgSO}_4$ . But even should some such narcotic effect be present, it seems certain that this cannot account for the entire picture.

## CHAPTER XLII

### FUNDAMENTAL STUDIES ON THE PHARMACOLOGY OF MERCURY DIURETICS \*

By RAYMOND N. BIETER, M.D., Ph.D.

AND

HAROLD N. WRIGHT, M.S., Ph.D.

#### GENERAL ACTION OF DIURETICS

**Introduction**—Studies were made in the Pharmacological Laboratory of the University of Minnesota under the direction of

Dr. A. D. Wright, M.D., Ph.D., who produced in blood means of drugs

studied with the ultramicroscope and also by means of other methods of experimentation. Hirschfelder and Wright<sup>1,2,3</sup> have shown that a number of antiseptic drugs, including arsphenamine and mercurochrome produce changes in the ultramicroscopic picture of the particles of rabbit's plasma. In general they have interpreted their results to mean that the drugs studied are adsorbed by the plasma particles. In so far as mercurials were included in their study their findings are confirmed by the studies herein reported.

The present chapter has to do with a study of several mercury preparations, with particular reference to the organic mercury diuretic drugs, namely, salyrgan and novasurol<sup>†</sup>. The attempt was made to study the fundamental processes involved in the production of their therapeutic action.

Diuretics may be assumed to act in one or more of the following ways: (1) Changes in the physico-chemical state of the blood and tissue colloids, (2) changes in the blood flow and permeability of glomeruli, and (3) changes in tubular permeability. While it would appear likely that changes in the kidney play a considerable rôle in the actual excretion of the urine, it would seem necessary, at least in some cases, that changes should take place first in the tissue and blood colloids, whereby water presumably bound to

\* A summary of the findings here reported was read before the Minnesota Branch of the Society of Experimental Biology and Medicine (Proc. Soc. Exp. Biol. and Med. 26: 551, 1929-1930) and the American Pharmacological Society, Chicago Meeting, March 1930.

<sup>†</sup> The salyrgan and novasurol used in these studies were obtained through the courtesy of the H. A. Metz Laboratories, Inc., New York.

**Conclusion.**—Unsatisfactory as our present knowledge of the physiological action of magnesium sulphate is, its use as outlined gives us a most effective therapeutic measure for successfully treating the frequently fatal condition of "pseudo or convulsive uremia" in acute glomerular nephritis.

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## GENERAL ACTION OF DIURETICS

plasma particles were definite and striking in all cases where either drug was used. These changes were as follows: (1) An increase in the average size of the particles; (2) what appeared to be a decrease in the number of particles visible; and (3) an increase in their brilliance or refractiveness. It was this change in brilliance that was so conveniently measured with the photometer. These changes are in agreement with those occurring when a lyophilic colloid changes toward a lyophobic colloid.

It very soon became evident that the per cent change in refractiveness as measured with the photometer varied and appeared to be greatest in those plasmas containing the drug that had been allowed to stand for several hours. Examples of this can be noted in the following four plasmas:

TABLE 64			
Normal heparin plasma	Novasurol added	$\alpha$ lyrgan added	Time added 1 hr 1 1/2 hrs 1 hr 6 hrs
R = 14	R = 15.0	R = 23.5	
R = 21	R = 27.1	R = 26.8	
R = 20	R = 27.0	R = 27.5	
R = 21			

This would indicate that these changes occur slowly and therefore time must be allowed to produce maximum effects. Consequently, in further experiments of this type the drugs were added to the diluted plasmas and readings of each were taken at one and a half and three hour intervals covering a period of up to ten hours. In addition another series of readings was taken using mercuric chloride. The solution of this drug was made up to 0.46 per cent so that its mercury content corresponded with that of novasurol. Salyrgan has a slightly higher percentage of mercury than novasurol but no correction for this was made.

**Plasma of the Dog**—Heparinized plasma was now collected from a series of frogs and from a number of dogs and the effects of the three mercury salts were studied on each plasma sample and compared to one another and to the normal heparin plasma. The results of this series of experiments with the ultramicroscope proved the above suggestion namely that the changes were progressive. They also brought forth another interesting point namely that with mercuric chloride the changes progressed most rapidly next in speed of action came novasurol and finally salyrgan showed the slowest rate of change. This might be associated with the clinical fact that salyrgan is less toxic and safer to use than novasurol. 80 shows a typical experiment upon one dog's plasma.

the proteins (bound water) is released and becomes available for filtration

In carrying on studies of the blood plasma some means of preventing coagulation must be employed. Therefore at the onset samples of blood were collected from *Rana catesbeiana* into (1) Heparin ( $\frac{1}{4}$  mg per cc of blood) (2) potassium oxalate (2 mg per cc) and (3) sodium citrate (2.5 mg per cc). These samples were centrifuged, the plasma pipetted off and diluted 1 to 5 with specially prepared particle free 0.75 per cent physiological saline. The diluted plasmas were then compared with each other and with plasma collected in the same manner but without the use of an anticoagulant under the ultramicroscope. From these experiments it was found that blood the coagulation of which was prevented with heparin yielded a plasma closest to the normal where no anticoagulant was used. In other words their ultramicroscopic appearances were almost the same. For this reason heparin plasma has been considered the standard in further experiments.

The criterion used to make these determinations was the general appearance of the particles, that is whether they were large or small, whether they reflected the light markedly or only slightly and whether Brownian movement was brisk or sluggish. For determining the amount of light reflected that is the refractiveness of the field, the wedge photometer of Hirschfelder and Wright was used. This gives nearly quantitative comparisons between the various samples of diluted plasma with and without the addition of the mercury salts. The photometer consists of the chamber of a long wedge colorimeter filled with an opaque solution (diluted non waterproof India ink). The wedge is moved across the top of the ocular of the ultramicroscope until the light cone is just completely obliterated. This point in centimeters from the narrow

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tion a greater

#### Plasma of the

**Frog** The effects of novasurol and salyrgan were first studied upon frog's plasma. Both drugs were made up in 0.1 per cent concentration in 0.75 per cent NaCl. This gives 0.01 mg per 0.01 cc. To 1 cc of frog's plasma diluted with  $\frac{1}{4}$  cc of 0.75 per cent NaCl solution was then added 0.02 to 0.04 mg of either novasurol or salyrgan. This amount of the drug is comparable to the concentration produced when 1 to 2 cc of a 10 per cent solution of either drug is injected intravenously in a patient assuming that the circulating blood has a volume of 5 liters.

Following this the diluted plasmas and the diluted plasmas plus novasurol or salyrgan were observed under the ultramicroscope and compared. The changes in the ultramicroscopic appearance of the

Six hours later another sample of plasma was obtained from the same patient. At this time the  $n_D$  was 18.2 or a 66 per cent increase in refractiveness *in vivo*. During the twenty four hours previous to the administration of the novasurol the patient voided 175 cc of urine. In the five hours following the novasurol the urine volume rose to 750 cc.

**Discussion of the Experimental Facts** The changes in the particles of the plasma solutions described above namely an increase in size of the particles and a marked increase in their brilliance or refractiveness are changes that correspond with those occurring when a lyophilic (water loving) colloid becomes lyophobic (water repelling). According to Krut<sup>4</sup> these changes are due to two processes. One is a decrease in the electric charge a change toward neutralization and the other is a decrease in hydration. For complete precipitation of a protein solution these two changes must take place, either one may occur first but either alone is not sufficient. In the precipitation of a protein in solution with ammonium sulphate the addition of the first small amount is thought to neutralize the charge and the addition of further large amounts dehydrates the protein particles and then precipitation occurs. With a mercury salt these effects can be produced in the same manner.

In our experiments we have used much smaller amounts of the mercury salts and no precipitation whatever has occurred. In the light of what is known of the precipitation of proteins with salts as described above it is thought that the first thing occurring is somewhat of a neutralization of the electric charge. But from what we know of this phenomenon it occurs rapidly. Because our

inclined to believe that this involves a dehydration. Further support for this belief is obtained from clinical experience with these mercury diuretics namely that they cause primarily an increase in the water output which however does not occur immediately after administration but shows a gradual increase reaching a

Sollmann that the diuretic effects were due primarily to the mercury ion.

If the authors experimental findings mean a change in the



## PHARMACOLOGY OF MERCURI DIURETICS

In this experiment the three drugs salyrgan, novasurol and mercuric chloride, in the percentage solutions described above, were added to one set of diluted plasma samples (dilution 1 to 40), 0.04 cc per cc of plasma, and to another set of diluted plasmas, 0.02 cc per cc of plasma. In both series the results were identical except that in the plasmas receiving the smaller amounts of the drug, the changes occurred more slowly and did not progress quite as far in the seven and a half hours of the experiment. As can be seen from Table 89, mercuric chloride produced a maximum effect (an increase in the R of 45 per cent) in about three and a half hours, novasurol a maximum effect (increase in R of 37 per cent) in about six hours, and salyrgan a maximum effect (increase in R of 28 per cent) in about seven and a half hours.

TABLE 89—SHOWING THE EFFECTS OF SALYRGAN, NOVASUROL AND MERCURIC CHLORIDE UPON THE REFRACTIVENESS (R) OF THE HEPARINIZED PLASMA OF A DOG

Time 12 M	Normal	0.04 cc mercuric per cc plasma			0.02 cc mercuric per cc plasma		
		Salyrgan	Novasurol	HgCl <sub>2</sub>	Salyrgan	Novasurol	HgCl <sub>2</sub>
1 30 P M	R = 16	R = 17.5	R = 18.0	R = 21	R = 17.5	R = 19.2	R = 20.0
3 00 P M	R = 16	R = 18.5	R = 20.5	R = 23	R = 18.5	R = 20.0	R = 20.0
4 30 P M	R = 16	R = 20.0	R = 21.2	R = 23	R = 20.0	R = 21.0	R = 21.0
6 00 P M	R = 16	R = 19.5	R = 21.5	R = 23	R = 20.2	R = 22.0	R = 22.3
7 30 P M	R = 16	R = 20.2	R = 22.0	R = 27	R = 20.5	R = 23.0	R = 22.5

**Kidney Extract From the Frog**—To study the effects of these drugs upon other body colloids the frog's kidney was selected. The kidneys were perfused free of blood and then ground in 0.75 per cent NaCl solution and centrifuged. The supernatant opalescent solution was then treated as the plasmas in the above experiments. The same changes were noted with these colloid solutions as with the colloids of the blood plasma, that is, the particles observed with the ultramicroscope seemed to decrease in number but to increase in size and refractiveness.

**Plasma of Patients With Cardiac Decompensation.**—Further studies were now conducted upon human cardiac decompensated patients. The material for these experiments was generously donated by Prof George E. Fahr, of the Minneapolis General Hospital, Minneapolis, Minn. The results obtained in 1 patient are as follows. To a sample of plasma from heparinized blood, 0.02 cc of novasurol, 0.01 per cent per cc of plasma, was added. The normal plasma showed an R of 11. The plasma plus novasurol showed an R of 22.5 (100 per cent increase) at three hours and an R of 23 (120 per cent increase) at eight hours. This patient was given 1 cc of novasurol intravenously at a time when the normal R was 11.

The membranes used were viscose sausage casings of about  $\frac{1}{4}$  to  $\frac{3}{4}$  inch in diameter

Heparinized dog's plasma prepared as described above was used for these experiments. To 10-cc plasma samples were added varying amounts of mercuric chloride made up in distilled water. Because the effects noted with the ultramicroscope required from three to four hours to reach a maximum these plasmas were allowed to stand for this length of time. Then they were dialyzed with occasional gentle shakings for periods of from one and a half to four hours. In all of the experiments of this series the plasmas to which mercuric chloride had been added showed a greater amount of chloride in the dialysate than did the controls.

Typical experiments run as follows

TABLE 91

	10 cc norm plasma Mg	0 + 5 mg HgCl <sub>2</sub> Mg	10 cc + 5 mg no Hg ol
Chloride dialyzed in three hours	46.800	49.00	47.6
Per cent dialyzed	100.000	103.700	101.7
Chloride dialyzed in three hours	57.964	61.087	
Per cent dialyzed	100.000	105.400	

In the first experiment the plasmas were allowed to stand three hours before the dialysis was begun. In the second experiment the plasma stood for four hours. The chlorides were determined by the thiocyanate titration method of Volhard. In all cases the results on the HgCl<sub>2</sub> plasma were corrected for the amount of chloride added. The amounts of mercuric chloride and novasurol added to these plasmas to date have been much larger than the clinical concentrations used. Further work is being done using

believed that these changes represent primarily a dehydration.

2. These same drugs produce progressive decreases in the free surface of the plasma particles as measured by the ability of the plasma particles to adsorb rose bengal.

3. From blood plasma to which novasurol and mercuric chloride have been added (to date in amounts larger than therapeutic doses) a greater amount of chloride can be dialyzed than from normal blood plasma.

4. It is believed therefore that the mercury preparations act as diuretics due to their action upon body and blood proteins. This action is thought to be a progressive dehydration and liberation of chlorides which are thus made more available for kidney excretion.

## PHARMACOLOGY OF MERCURY DIURETICS

electric charge and, more especially, if they mean a dehydration, the surfaces of these plasma particles ought to show changes which lower surface tension, decrease the binding power of a protein in solution for rose bengal. Hirschfelder and Wright<sup>1</sup> have shown in a study of the behavior of antiseptics in albumin solutions that the amount of malachite green bound by a given mass of egg albumen decreases as the concentration of the protein increases. They interpret this as due to a dehydration of the protein micelles with increasing protein concentration and a corresponding decrease in the free surface.

It was therefore, thought worth while to study the adsorption of this dye by the plasma protein particles before and after the addition of varying amounts of mercuric chloride, novasurol and thyrigan. A progressive decrease in the free surface of the proteins was found over a period of about 48 hours. An experiment of this type is shown in Table 90.

TABLE 90—SHOWING THE PER CENT DECREASE IN FREE SURFACE OF THE PLASMA COLLOIDS OF A DOG PRODUCED BY  $HgCl_2$ , NOVASUROL AND THYRIGAN MEASURED BY THE ABILITY OF THE PLASMA COLLOIDS TO BIND ROSE BENGE

Time	Mr per 100 cc of plasma	Per cent decrease in free surface																	
		Mercuric chloride						Novasurol						Thyrigan					
		2	4	6	8	10	12	4	8	12	16	20	4	8	12	16	20		
3 hrs		6.1	10	10	7	12	7	12	7	0	0	0	0	0	0	0	0	0	0
5 hrs		7.3	9.3	12	7	15	0	16	0	0	0	0	0	0	0	0	0	0	0
8 hrs		6.3	10	0	12	3	1.7	16	7	2	3.2	6.8	9.0	6.0	1.2	2.4	4.0	6.0	9.2

From the fact that the change in the free surface is progressive over a period of hours, paralleling the changes observed with the ultramicroscope and the clinical occurrence of the diuresis, it seems probable that the essential step is a slow release of bound water (dehydration of the proteins) which then becomes available for filtration.

One other important action of mercury diuretics is to increase the urinary output of chlorides. If the explanation of the ultramicroscopic readings above is a decrease in the electric charge and a dehydration chlorides might also be liberated in this process and then become available for filtration. To study this phase of the problem, samples of plasma without and with additions of small amounts of mercuric chloride were dialyzed against distilled water.

## CHAPTER XLIII

### THE CLINICAL USE OF DIURETICS

By NORMAN M. KEITH, M.D.

**Introduction — The Choice of Diuretics** — The author's interest in the subject of diuretics was primarily stimulated by the inadequacy of the accepted methods of treating renal edema. In December, 1923, a patient under his observation, with chronic diffuse nephritis and general anasarca, failed to respond to the usual methods of treatment. Knowing that calcium chloride had been used successfully abroad by Blum and others<sup>1</sup> in cases of edema, he decided to give it a trial in this instance. The patient was given calcium chloride for three periods, each of a week's duration. During the first period,

diets<sup>19</sup> have a lower content of salt and water than the so-called salt-free diet of Widal, and the author has found it to be an important adjunct to diuretics in the treatment of edema<sup>1, 19</sup> (Table 92).

TABLE 92 — COMPOSITION OF DIETS LOW IN SALT AND FLUID

Type	Carbohydrate gm	Protein gm	Fat gr	Calories	Water cc	Sodium gm	Chlorine gm
Basal "salt-free"	190	40	65	1500	1300	1.15	1.60
1	150	40	60	1500	800	0.50	0.70
2	235	60	145	2500	900	0.77	0.68
3	300	60	120	2500	910	0.70	0.90
4	350	70	85	2600	850	0.68	0.65
5	345	80	90	2500	950	0.67	0.75
6	320	90	95	2500	860	0.65	0.78
7	275	100	110	2500	920	0.75	0.60

Later, ammonium chloride was substituted for calcium chloride, as it is less irritating to the stomach and just as effective as a diuretic. In April, 1924, a patient with renal disease and marked

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the abdominal organs satisfactory diuresis can be produced by the procedures mentioned. They have also proved effective in myxedema.

**The Prevention of Toxic Symptoms.**—The occurrence of obvious toxic effects such as stomatitis, diarrhea and dermatitis was very infrequent. They occurred relatively more often in cases of hepatic insufficiency than in any other single group of cases and usually followed injections of merbaphen. Mersalyl very rarely caused general toxic symptoms although in a few cases local necrosis occurred at the site of intravenous injection. This usually can be avoided by diluting the drug in 10 to 20 cc. of physiological solution of sodium chloride or in the same amount of the patient's own serum. The most frequent toxic effect was definite renal insufficiency; clinical symptoms of a toxic nature were usually absent. As one would naturally surmise renal insufficiency occurred most frequently in cases of glomerulonephritis but it also occurred in a considerable number of cases of hepatic disease. Fortunately it was a temporary dysfunction in the majority of instances; the value for blood urea fell to normal and the excretion of phenolsulphone phthalein rose before dismissal of the patients. Severe acidosis when caused by ingestion of ammonium chloride or calcium chloride may be accompanied by marked renal insufficiency. By careful administration of these salts such an untoward event can be prevented.

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sometimes occur but disappears quickly when administration of the salt is discontinued. Dehydration resulting from both a low intake

there seems to be less tendency to toxic reactions than in cases in which there are either renal or hepatic lesions. This finding is in agreement with those of previous observers.

**Experiments on Normal Subjects.** In order to obtain under controlled conditions more definite information as to the action of diuretics a series of experiments was carried out on 12 normal persons (Fig. 162). The diets were the same as those given to patients with edema with the addition of 800 cc. of fluid. A control period

under investigation was withheld. During the experimental period the volume of urine, the total excretion of chlorides, the total fixed base in the urine and the total nitrogen in the urine were determined daily. The trial substances administered were ammonium

general anasarca was given ammonium chloride with good diuretic response.<sup>16</sup> In 1933 the patient was still free from edema and was in good general health. If edema persisted in any case after the use of these acid salts a trial was made of the organic compound of mercury merbaphen. The combined effect of ammonium chloride and merbaphen was often more striking than when these substances were administered singly.<sup>17, 20</sup> Chronic lipid nephrosis was the type of renal disease that responded most satisfactorily to these diuretics although in certain cases of chronic glomerular nephritis with edema a satisfactory response was obtained. In cases of the latter type care must be taken that the concentration of urea in the blood is not greatly increased and that the organic compound of mercury does not cause hematuria. In 1 case in which hematuria occurred after the first injection of merbaphen an injection

nitrate. However the experiments represented by Fig. 1(2) involved 12 normal persons only. Actually in practice of these acid salts which the most efficient indicate the specific diuretic action. In this connection it should be pointed out that Osman produced diuresis in cases of renal edema by the use of large doses of alkaline salts.

**Clinical Types of Edema.** In cases of renal edema in which acid salts and organic compounds of mercury are contraindicated compounds of caffeine such as synthetic theophyllin (theocin) and euphyllin may be used. It should be noted that digitalis might also be used in the author's experience of cardiac decompensation.

The significance of diuretics in the treatment of cardiac edema is becoming generally recognized. One of the author's patients who

— 1 of mercury  
found in  
liters<sup>21</sup>  
human  
excretion  
by the

use of diuretics

In three conditions in which ascites occurs namely cirrhosis of the liver, polyserositis or Pick's disease and malignant disease of

and disappears quickly after administration of the nitrate is discontinued<sup>10</sup>

In later experiments on dogs and normal persons the combined effects of ammonium chloride or ammonium nitrate and organic compounds of mercury were studied. Excretion of water chloride and fixed base was much greater than when these were administered singly.

**The Action of Diuretics**—In any consideration of the action of these diuretics a general and a renal effect must be considered.<sup>7,9</sup> The acid chlorides alter the acid base equilibrium and increase the concentration of plasma chloride.<sup>18,20</sup> Both factors aid diuresis.<sup>7,8</sup>

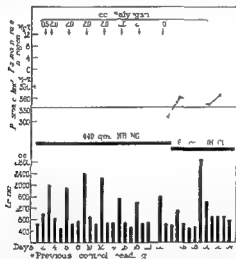


FIG. 163.—A case of cirrhosis of the liver with ascites in which the patient was aged nineteen years. Restoration of falling diuresis, increase in plasma chlorides by the substitution of ammonium chloride for ammonium nitrate are shown.

When the concentration of plasma sodium was increased by ingestion of a sodium salt spontaneous polyuria occurred. Blumgart<sup>5</sup>



acetate digitalis sucrose, urea euphyllin, sodium nitrate, ammonium nitrate, ammonium chloride and merbaphen. The results are shown in Fig 162. It should be noticed that ammonium acetate and digitalis had little diuretic effect that urea produced typical diuresis of water and that euphyllin and sucrose caused slight increase of excretion of water chloride and fixed base. Sodium nitrate caused an increase in excretion of water chlorides and fixed base, whereas ammonium nitrate caused similar, but increased excretion. Ammonium chloride likewise produced marked excretion of water fixed base and chlorides, excretion of chloride was due in part to the large intake of chloride. Of all these nine substances, merbaphen produced the most rapid diuresis.<sup>16b</sup>

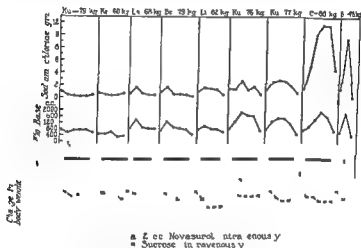


FIG 162 — Comparison of the action of certain substances on the output of water chlorides and fixed base in the urine of normal persons. The daily intake of food and water was the same throughout each experiment.

The excretion of nitrate in the urine following ingestion of ammonium nitrate by a normal person amounted to from 80 to 90 per cent.<sup>22</sup> The concentration of nitrate nitrogen in the blood plasma rose to from 2 to 3 mg per 100 cc. The excretion of nitrate was similar in cases of chronic nephrosis but the concentration in the blood increased. In 1 case of diffuse nephritis the nitrate produced diuretic effects but failed to be excreted in suitable amounts so that marked retention of nitrate occurred in the blood, the concentration reaching 19 mg per 100 cc. In spite of the toxic effect the patient made a good recovery. Since this occurrence the use of a simple method devised by Whelan for determining the nitrates in the blood has allowed such toxic effects to be prevented. Methemoglobinemia occurs rarely, does not cause inconvenience.

The ideal diuretic has yet to be discovered. In the last fifteen years, experimental work and clinical observation have added much to knowledge as to the action and therapeutic results of various types of diuretics. This should give much hope for continued development in the future.

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expressed the belief that an optimal concentration of sodium in addition to that of chloride in the plasma is important for diuresis and may in part be the reason for production of diuresis by alkaline salts. Stehle in his experimental work with compounds of mercury stressed their general tissue action because there is a definite latent period before diuresis begins. The experiments of Govaerts and of Christian and Bartram<sup>6</sup> on the other hand emphasized the marked renal action in diuresis caused by mercury. Hartman<sup>12</sup> has tried intravenous injection of acacia in stubborn cases of lipid nephrosis and has been able to produce diuresis. In his opinion the diuresis was caused by raising the osmotic pressure of the plasma.

Recent advances in renal physiology suggested that different types of diuretics might have specific actions on the glomerulus or tubule.

able to show  
effects on the

similar results in cases of cardiac disease with edema. Because there is some question as to the exact significance of creatinine clearance by the kidney the author does not feel that the results of Schmitz and Herrmann have yet established the fact that mercury exerts its diuretic action by diminishing reabsorption of water by the tubules and ephyllin its diuretic action by increasing glomerular excretion. Experiments of Smith and his co-workers<sup>10</sup> with the renal excretion of certain sugars has suggested that these sugars pass through the glomerulus and are not reabsorbed by the tubules. It is of interest that Herrmann<sup>13</sup> has found that the ratio of the creatinine to the xylene clearance is increased when mersalyl is used but little altered when caffeine and compounds of digitalis are used.

Potassium salts have been known for many years to have a dehydrating effect on the animal organism. Wilks and Taylor in 1803<sup>20</sup> administered potassium nitrate by mouth in a case of nephritic edema with success. The toxic effects of potassium salts when administered by vein deterred physicians for many years from using them in clinical medicine. Barker<sup>2</sup> has introduced the use of potassium chloride by mouth in cases of cardiac and renal edema. He has seen no toxic effects and the diuretic effect in some cases has been satisfactory. The author has confirmed his findings in a few cases. This action of potassium chloride suggested to the author a trial of potassium nitrate in place of ammonium nitrate,

has been present and it has proved a valuable addition to diuretic drugs. Further studies as to its action on the blood and urine are being carried out.

## CHAPTER XLIV

### NERVOUS RENAL CONTROL AND RENAL SYMPATHETIC TONY

By LEONARD G. ROWNTREE, M.D., M.D.

WALTERMAN WALTERS, M.D., M.D.

AND

WINCHELL McK. CRAIG, M.S., I.V.C.S.

**Introduction** —What part do the renal nerves play particularly the sympathetic in the control of the kidney? What are the functions of the sympathetic in the control of such a step?

The interest in this subject with one of the authors (R.G.) dates back a long time. Some twenty years ago experiments were carried out in the laboratory of Dr. John Abel in the course of which subsequent to injection of phenolsulphonephthalein into rabbits and dogs one kidney was denervated and the output and character of the urine from the two sides contrasted. From the denervated side striking diuresis was obtained the urine being of low specific gravity and of a pale pink color indicating a slight alkalinity, whereas from the intact kidney the amount of urine was small the specific gravity high the color yellow and the reaction acid.

of the renal nerves outside the kidney and what is the distribution of the nerves?

What is the effect of the volume of urinary output upon the composition of the urine and on the total amount of work done by the kidney?

3. Hitherto the leading principle for much research clinical as well as physiological has been a comparison of the composition of the urine with that of the blood. On this basis light has been thrown upon important phases of renal function. The development at present points toward a period of concentrated interest in the balance between nervous and hormone regulation.

1897-1901  
 28 WIDAL, F. AND JAVAL, A. 1903 La cure de déchloruration Son

researches (Smirnow and others and most recently Kaufmann and Gottlieb<sup>14</sup>) demonstrating the presence of an extensive unmyelinated innervation of the parenchyma of the tubular epithelial cells in addition to the well recognized vascular innervation. Smirnow's figures are frequently reproduced by Stehr<sup>15</sup> and by Mollenhuth<sup>16</sup>.

and experimental results in regard to character of renal pain. While there is no doubt about the production of pain from the renal pelvis and about the absence of pain sensations from the renal parenchyma it is difficult to know to what extent pain is produced by the renal capsule. Surely stretching the capsule is sometimes concomitant with pain in the renal region, but times not, and renal pain might be present when the kidney is contracted and the capsule adherent. There is full agreement that pull upon the kidney is painful, and surgeons of excellent judgment consider much renal pain as originating in the perirenal plexus.

**Diuresis Following Denervation of the Kidney** The nephrotomy is sometimes fatal, reflex anuria well known from instances of stone in one renal pelvis and also observed after the introduction of a ureteral catheter in the pelvis is of theoretical importance as

absolute denervation through autotransplantation is compatible with satisfactory renal function and normal life (Quimby, Milliken and Karr,<sup>16</sup> Williamson<sup>17</sup> and others). The next important question concerns the interpretation of the diuresis following complete denervation or rather of the changes in the excretion of solids concomitant with the diuresis. Marshall and Kolls<sup>3</sup> found these changes fully explainable on the basis of alteration of renal blood flow and saw no necessity to assign any specific secretory inhibitory action to the splanchnic nerve. Cushny<sup>2</sup> took the same standpoint. The excretory features studied by Marshall and Kolls besides urine volume, included the elimination of phenolsulphonaphthalein, creatinine, urea and chlorides. The absolute elimination of phenolsulphonaphthalein and creatinine was not altered by the diuresis following one-sided section of the splanchnic or homolateral extirpation of the adrenal while urea and chlorides were eliminated in increased amounts, the chloride concentration even being higher on the denervated side. This high chloride concentration together with high urine volume on the operated side is particularly marked after the denervation of the kidney. The diuresis is numerous in its results.

4. Discussing the interest upon the possibility of influencing the nervous mechanism of the kidney surgically or otherwise different problems present themselves. Three different indications claim consideration (a) Relief of pain (b) improvement of function by relaxation of spasm and (c) relief of anuria of reflex nature so called reno-renal reflex anuria.

To none of these questions is it possible at present to give a satisfactory answer.

**Innervation of the Kidney** Our anatomical knowledge is presented by Renner in the monographic work by Muller<sup>18</sup> by Stohr<sup>23</sup> and by Kuntz.<sup>1</sup> Among the abdominal organs the kidneys possess a nerve supply which in richness is second only to the adrenals. According to Quinby<sup>21</sup> this cannot be fully severed by perivascular stripping alone some fibers running within the vessel walls. Complete denervation can be obtained only by section of the renal pedicle followed by reimplantation of the kidney by vascular suture. Langres gives the following description. The extrinsic nerve supply of the kidney is derived from the renal plexus which extends from the aortic plexus along the renal artery to the hilum of the kidney. The renal plexus is made up of branches arising from the center of the semilunar ganglion the lesser splanchnics and major splanchnics a branch arising from the first lumbar ganglion and small branches arising from the small ganglion which lies on the posterior aspect of the superior mesenteric artery. The renal plexus is also joined by one or more slender rami from the lumbar portion of the sympathetic trunk according to some authors. Vagus branches run directly to the renal plexus in many but not in all cases. Direct vagus branches seem to occur more commonly on the right than on the left side. Preganglionic fibers supplying the kidney are present in all the splanchnic nerves. The afferent fibers supplying the kidney are derived from the fourth to the twelfth thoracic segments but clinical evidence seems to indicate that they are derived mainly from the tenth eleventh and twelfth thoracic segments.

The innervation has been analyzed in detail by Ellinger and Hirt<sup>2</sup> who describe three nerve groups: (1) The greater splanchnic (2) the lesser splanchnics (*nervi renales superiores*) and (3) fibers leaving the sympathetic trunk in the lower thoracic and lumbar segments (*nervi renales inferiores* or *unteren Grenzstrangfasern*). Ellinger and Hirt claim a separate functional effect by each nerve

the vagus  
fibers  
to the  
renal

pelvis and to the capsule is well known. Of special interest are the

At least a suggestion of the normal stimulus for the reflex regulation of urinary secretion may be seen in another result obtained by Bayliss and Fee. These workers used an innervated kidney-heart lung preparation, the kidney was left with intact nerve supply

kidney provided by the heart lung preparation increased as did the urine flow, changes possible only through reflex dilatation of the vascular bed of the kidney. Similar reflex vascular dilatation in the kidney has been obtained by Hevman following increased pressure within the carotid sinus. (See Volhard page 391.)

**Clinical Aspects**—During the wave of antineuralgic perivascular sympathetic stripping which swept over about 1920, Papin and Ambard<sup>10</sup> carried out the first renal sympathectomy on man. The operation was undertaken first in 1921. Six instances were reported in 1921 (republished in the entry 1924). The conditions for which the operation was undertaken were diagnosed as slight hydronephrosis and renal ptosis. All 6 patients suffered by these patients the authors found to be exactly reproduced by distending the renal pelvis during pyelography. Four patients were relieved of their pain, 2 were not benefited by the operation. The operation consisted in resection of the nerve anteriorly and posteriorly to the renal pedicle. This necessitated extensive freeing of the kidney. At the end of the operation the artery and vein should be completely stripped of all surrounding nerve filaments. Decapsulation and nephropexy were performed as a part of the operation in all instances. The operation was not considered difficult, but care had to be exercised not to injure the renal vein.

Th—  
symptoms  
Leguen  
unilateral

impairs its functional capacity, it may be done tentatively as a preliminary procedure. Harris and Harris<sup>11</sup> of Sydney, in the last five years have performed this operation for the relief of renal pain on 28 patients with most satisfactory results. They have elaborated the painful condition in which they have found the operation indi-



Marshall and Crane<sup>14</sup> to previous results added data as to the behavior of carbonates ammonia sulphates and phosphates. The carbonates behaved much like the chlorides ammonia like creatinine and sulphates and phosphates like urea. Ellinger and Hirt<sup>15</sup>

ments demonstrate that similar diuresis with its sequences does not occur after section of the greater splanchnic nor of the fibers from the lower sympathetic trunk (nervi renales inferiores). To  
 stic action  
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 has been

presented

**Stimulus for Reflex Regulation of Urinary Secretion**—What is the central or reflex stimulus whereby the nervous control of urinary secretion is brought to function? Dieter in this volume discusses the reflex arch and exemplifies the mechanism. But cooling of the skin or pinching the hind limb surely does not represent the normal stimuli by which continuous control is exercised. How far has the balance between nervous and hormone control been elucidated? Just as in blood pressure studies investigative efforts have been concentrated upon the balance between adrenalin discharge and splanchnic stimulation so the problem of the control of urinary secretion centers on the splanchnic and the pituitary though the adrenals too have to be considered (Tournade and Hermann<sup>16</sup>). As in the studies of the regulation of blood pressure (Volhard page 388) so even here development in experimental technique made possible more precise formulation of the problem. Studies by Starling and Verney<sup>17</sup> on the isolated kidney provided with cir  
 does in a  
 mentally  
 low in total solids  
 that of the perfus  
 erfusion fluid both  
 in experiments by Starling and Verney and by Bayliss and Fee<sup>18</sup> increased the chloride concentration in the urine and augmented greatly the total amount of chlorides excreted. The addition of blood fresh from an animal with preserved circulation through the head produced the same effect in the experiments of Bayliss and Fee. Verney<sup>19</sup> by including the heart lung kidney preparation also the head and neck likewise registered increased concentration of the chlorides but failed to obtain an increase in the absolute amount

twenty years duration. An adenocarcinomatous polyp was removed from the duodenum. Convalescence was uneventful. Two months later he developed a chronic infectious arthritis and returned to the clinic for

attributed to the renal pelvis resection alone.

cated as a clinical entity for which they offer the name renal sympathetico tonus. These authors have further performed the operation once for 'essential hematuria' and once for parenchymatous nephritis. For conditions of this latter type Tietze<sup>1</sup> emphasized the satisfactory results obtained by decapsulation alone. In the Mayo Clinic, 2 of the authors (W. and C.) have performed renal sympathectomy in selected cases.

From the point of view of the internist renal sympathectomy presents quite a different problem viz. the increase of urinary secretion through release of vasoconstriction. During the last five years ever since results were obtained through sympathectomy in cases of arthritis the possibility of increasing the circulation in renal disease by the use of a similar operation has seemed worth considering. Consequently it was advocated by one of the authors

known sequelæ polyuria etc. have been observed. As a characteristic feature may be emphasized an increased functional irritability or an exaggerated response to additional demands.

Denervation of the kidneys was also done in animals in which experimental lesions had been induced. This included 2 dogs with uranium nephritis and 2 dogs with marked reduction of renal substance by the method of I. M. Allen and of Marx. In both uranium dogs an improvement in urinary and phenolsulphonephthalein output and a decrease in nitrogen retention were noted immediately after denervation. In dogs with approximately 30 per cent of remaining renal tissue improved handling of excessive nitrogen feeding was evident after the operation. Caldwell in rabbits subjected to acute uranium nephritis found no immediate effect from denervation if the operation was performed within four days in other words before spontaneous recovery began.

On the clinical side sympathectomy has been carried out in 4 patients. Decapsulation in addition to the sympathectomy was simultaneously done in the first 2 cases. The case reports are as follows

L. E. and A. T. 1918

operated upon for a small hydronephrosis and for relief of pain. It would seem worth while to try this procedure in cases of chronic nephritis with oliguria and retention. It could also be tried early in glomerular nephritis where Volhard believes vasoconstriction to play an important role. Milder measures than sympathectomy might suffice for the release of vasoconstriction. This might be obtained through the use of diathermy to the regions of the sympathetic ganglia. The use of diathermy to the peripheral vessels has been used in the clinic and Eppinger has reported good results abroad. Sympathetic analgesia at these levels might also be of value. This procedure is not without danger and pregarious. This procedure is not without danger.

for periods of at least one month. When operation is contemplated preliminary information may be derived either by diathermy by injection of the ganglia or by the use of spinal anesthesia at this level.

The interest of the internist in the development of this work is stimulated by the physiologist. In a plea for further clinical investigation of the effect of section of the splanchnics on the failing kidney Fulton<sup>4</sup> writes: "The surgeon then who undertakes to

is destroying a part of one of the oldest and most fundamental systems regulating the bodily economy. He may be called upon to cut the splanchnic nerve in order to assist the failing kidney or to remove the abdominal sympathetic chain to alleviate the distressing symptoms of Hirschsprung's disease.

The rationale of these two operations is obvious.

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CASE 4—(709030) J S N, a white male aged twenty-one years

euphyllin ammonium nitrate magnesium sulphate pilocarpine *etc.*

blood cells +++

TABLE 93

	Right Kidney	Left Kidney
Volume cc	10 000	10 000
Specific gravity	1 013	1 015
Albumin grade	2	2
Nitrogen per cent	0 93	0 86
Non protein nitrogen	0 89	0 85
Protein nitrogen	0 04	0 01
Chlorides	0 34	0 33
Casts		
Hyaline	1	Occasional
Granular	1	Occasional
Cellular	1	0
Leukocytes	1 to 9	1 to 7
Erythrocytes	3	3
Phenolsulphonaphthalein		
Time of appearance minutes (three to five minutes upper limits of normal)	5	5
Amount per cent	III	6
Indigo-carmin		
Time of appearance minutes (five minutes upper limits of normal)	7	7
Concentration of dye grade	3	3

The results in 3 of these 4 cases are not striking however 2 patients were moribund at the time of operation. In the fourth case the clinical condition of the patient with subacute glomerular nephritis is excellent at the present time. The third case was

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